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EXPERIMENTAL PIGMENT CIRRHOSIS DUE TO COPPER POISONING

ITS RELATION TO HEMOCHROMATOSIS *

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In 1921, Mallory, Parker and Nye [1] published the results of experiments on rabbits and other animals in which they claimed to have produced hemochromatosis in its early manifestations by means of chronic poisoning with copper salts. Mills [2] (1924) reported sixteen cases of hemochromatosis that had come to autopsy at the Boston City Hospital during the past twenty-five years. The remarkable number of ten cases had occurred in a single year, 1922 to 1923, while according to Futcher,[3] in seventeen years only three cases had been seen in the medical wards of Johns Hopkins Hospital, and according to Howard and Stevens,[4] only eighty-one cases had been reported in the literature up to 1917. In spite of the unusual number of cases seen by Mills [2] in one year, hemochromatosis continues to be a rare disease. In the sixteen cases which Mills reported, ten patients gave histories of contact with copper or brass in their daily occupations over periods ranging from twelve to thirty-six years.

The present work was undertaken with the desire to repeat, and perhaps to enlarge, on the experiments of Mallory and his associates, especially since their observations were so new and extraordinary.

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1. Mallory, F. B.; Parker, Frederic, Jr., and Nye, R. N.: Experimental Pigment Cirrhosis Due to Copper and Its Relation to Hemochromatosis, J. M. Research **42**:461, 1921.

2. Mills, E. S.: Hemochromatosis with Special Reference to Its Frequency and Its Association in Women, Arch. Int. Med. **34**:*292* (Sept.) 1924.

3. Futcher, Thomas B.: Hemochromatosis with Diabetes Mellitus, Am. J. M. Sc. **133**:78, 1907.

4. Howard, C. P., and Stevens, F. A.: The Iron Metabolism of Hemochromatosis, Arch. Int. Med. **20**:896 (Dec.) 1917.

Von Recklinghausen [5] gave the first accurate description of the disease, and proposed the name hemochromatosis. He was also the first to recognize the presence in the diseased organs of two kinds of pigment—an iron-containing pigment, hemosiderin, and a pigment which fails to give the iron reaction and for which he coined the name hemofuscin. Perhaps the great interest which this disease has aroused is due to the presence and peculiar distribution of the two pigments, to the coincident development of cirrhosis, and to the fact that the etiology continues to be a matter of speculation and an interesting subject for experimental research.

The various theories as to the etiology of the disease are well summarized by Sprunt,[6] Howard [7] and others. We shall therefore treat briefly only two of the more important ones. The idea that hemochromatosis is due to increased blood destruction was first introduced, in 1895, by Marie,[8] Acard,[9] Dutournier,[9] Jeanselme,[10] Anschütz,[11] Ridder,[9] Opie,[12] Abbott [13] and others have supported this theory or modifications of it. Biondi,[14] Schurig [15] and Muir and Dunn [16] have attempted to produce hemochromatosis experimentally by various methods of blood destruction, but succeeded only in producing the picture of secondary anemia with more or less hemosiderin in the spleen, kidneys, bone marrow, and in some instances, in the liver. By the transfusion of rabbits over long periods, Rous and Oliver [17] produced marked pigmentation of the spleen, liver, bone marrow and kidneys with hemosiderin, with

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5. Von Recklinghausen: Ueber Hamochromatose, Tagebl. d. Versamml. deutch. Naturf. u. Aertze., 1889, p. 324.

6. Sprunt, T. P.: Hemochromatosis, Arch. Int. Med. **8**:75 (July) 1911.

7. Howard, C. P.: Hemochromatosis, Oxford Med. **4**:215, 1921.

8. Marie, P.: Sur un cas de diabète bronzé suivi d'autopsie, Semaine méd. **15**:229, 1895.

9. Acard, quoted from Sprunt (footnote 6).

10. Jeanselme: Hematologie et pathogene du diabète bronzé, Bull. et mém. Soc. méd. d. hôp. de Paris **14**:179, 1897.

11. Anschütz, W.: Ueber den Diabetes mit Bronzefärbung der Haut, Deutsches Arch. f. klin. Med. **62**:411, 1899.

12. Opie, E. L.: A Case of Hemochromatosis: Relation of Hemochromatosis to Bronzed Diabetes, J. Exper. Med. **4**:279, 1899.

13. Abbott, Maude: Pigmentation of Cirrhosis of the Liver in a Case of Hemochromatosis, J. Path. & Bact. **7**:55, 1901.

14. Biondi, Cesare: Experimentelle Untersuchungen über die Ablagerung von eisenhaltigen Pigment in der Organen infolge von Hämatolyse, Beitr. path. Anat. u. allg. Pathol. **18**:176, 1895.

15. Quoted from Rous and Oliver: J. Exper. Med. **28**:629, 1918.

16. Muir, Robert; and Dunn, John S.: Retention of Iron in Organs in Anemia, J. Path. & Bact. **19**:417, 1915-1916.

17. Rous, Peyton, and Oliver, Jean: Experimental Hemochromatosis, J. Exper. Med. **28**:629, 1918.

lesser amounts of pigment in other organs including the suprarenals. Some cirrhosis developed in two rabbits, but it was thought to be spontaneous.

Anschütz [11] reported a case of hemochromatosis and summarized twenty-four cases of the disease which had been reported in the literature up to 1899. He was much perplexed on not finding anemia or evidences of increased hemolysis in these cases. Blood count records by Jeanselme,[10] in two cases of Futcher's [8] and in Osler's [9] case have all been normal with a hemoglobin average of 90 per cent or over. Clinical or postmortem evidence has not been found to indicate undue hemolysis in this disease.

The most recent theory was introduced in 1900 by Meltzer,[18] who realized that abnormal blood destruction could not be the cause of the pigmentation. He believed that the primary trouble is with the mechanism of metabolism concerned in the removal of iron from the body. Parker,[19] Gaskell [20] and his associates agree with this idea. Iron metabolism studies made in cases of hemochromatosis by Howard and Stevens,[4] McClure,[21] Fowell [22] and Garrod [20] have all shown a slight, but definite, retention of iron. These authors conclude that hemochromatosis may depend, therefore, on some injury to the liver resulting in a hepatitis, which in turn may cause a disturbance of the iron metabolism followed by a slight, but prolonged, retention of iron in the course of the normal hemolysis of red cells.

The next question which arises concerns the initial lesion in the liver. What is the agent that produces a slight but constantly acting injury to the liver cells over a period of fifteen, twenty or even thirty years and thus interferes with their ability to handle iron?

Mallory and his associates have attempted to answer this question and have tried to substantiate their claims by experimental methods. They make the interesting suggestion that hemochromatosis is due to chronic poisoning with copper. According to their ideas, copper is the agent which injures the hepatic cells and interferes with the metabolism of iron. It is suggested that copper enters into combination with the iron during some stage in the process of breaking down the hemoglobin molecule forming a cuprohemol compound (Kobert).[23] Mallory [1] and his co-workers believed that the noniron reacting pigment, hemofuscin, contains this cuprohemol compound.

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18. Meltzer, S. J.: The Pathogenesis of Hemochromatosis, M. Rec. **57**:43, 1900.

19. Parker: Case of Bronze Diabetes, Brit. M. J. **2**:1052, 1903.

20. Gaskell, quoted from Howard and Stevens (footnote 4).

21. McClure, C. W.: Metabolism in a Case of Hemochromatosis, Arch. Int. Med. **22**:610 (Nov.) 1918.

22. Fowell, P. H. C.: Iron in the Blood, Quart. J. Med. **6**:179, 1912.

23. Kobert, Robert: Lehrbuch der Intoxikationen **2**:407, 1906.

In the experimental study by Mallory, Parker and Nye,[1] twenty-two rabbits were fed small quantities (0.2 Gm.) of copper acetate mixed in their food over a period of a few weeks to eleven and a half months. Three cases of cirrhosis occurred in this group, the first at five and a half, and the second at six and a half and the third at eleven and a half months. In these three animals as well as in the others, the liver cells were loaded with small yellow granules or hemofuscin. The granules began to appear within two or three weeks and were numerous in from two to three months. None of the hemofuscin, even at the end of eleven and a half months' feeding, had changed to hemosiderin. Grossly, the livers were chocolate brown, except when modified by the presence of jaundice.

A few granules of pigment were found outside of the liver in endothelial leukocytes of the mesenteric lymph nodes, and in the spleen and bone marrow.

There was no evidence of anemia, and examination of the blood revealed a normal condition at all times.

Experiments on other animals showed that the pigmentation develops much more slowly in guinea-pigs than in rabbits. Only a moderate hepatic sclerosis was present in animals fed for over a year. According to Mallory and others, white rats show pigment in the liver about as quickly as rabbits, but they are slower to show evidence of cirrhosis. Mallory and his co-workers also fed a ringtail monkey copper acetate for five and a half months. A fair degree of pigmentation of the liver cells resulted, about half the granules reacting like hemofuscin, the other half giving the iron reaction.

METHODS

During the past year and a half we have conducted a series of experiments on chronic copper poisoning in rabbits, white rats and sheep. Some of the animals were given copper acetate in their food, others received subcutaneous injections of weak solutions of the copper salt, while a third group were given a mixture of copper acetate and alcohol by stomach tube. Seven rabbits were given daily from thirty-three to forty-one weeks 0.25 Gm. each of dry copper acetate powder mixed with slightly moistened rolled barley. Seven rabbits were fed copper acetate in the same manner as the first group for varying periods from eleven to twenty-four weeks after which they were given subcutaneous injections of 1 per cent copper acetate over a period of approximately twelve weeks, except two of the animals that died within twenty-four hours following injections of 5 cc. of 1 per cent copper acetate solution. A group of five rabbits were given subcutaneous injections only of copper acetate over periods of time ranging from one to ten weeks.

Thirty-eight white rats were fed for forty-two weeks on a balanced diet, prepared in Dr. Addis' laboratory, consisting of corn meal, 68 per cent; linseed oil cake, 10 per cent; casein, 10 per cent; alfalfa, 2 per cent; lard, 5 per cent; cod liver oil, 3.2 per cent; bone ash, 1.5 per cent; sodium chloride, 0.005 per cent to which a 1 per cent solution of copper acetate was added in quantities to make from 0.018 to 0.04 Gm. of the copper salt per rat.

Fourteen rabbits were given daily by stomach tube 20 cc. of a mixture consisting of four parts of 50 per cent alcohol and one part of 5 per cent copper acetate solution. Although every precaution was taken to prevent aspiration of the material, many of the animals developed purulent bronchitis and later, bronchopneumonia within a few weeks after the experiment was started. Four animals survived sufficiently long to develop some early lesions in the liver. One survived fourteen weeks, another twenty and two others for thirty-two weeks.

White rats are more resistant to respiratory infections than rabbits, consequently we did not have any difficulty in administering to them by stomach tube from 3.5 to 4 cc. of the alcohol-copper acetate mixture daily for a period of from ten to twelve months. Twenty animals were used in this series.

Two sheep (wethers), weighing 80 and 90 pounds (35.3 and 40.8 Kg.) respectively, were injected subcutaneously three times a week for a period of six months with a mean dose of 2.5 cc. of 1 per cent copper acetate solution. At the end of this period both animals were killed and autopsied.

When an animal died or if, purposely, it was killed, an autopsy was performed at the earliest possible moment and a description of the gross appearance of the organs was made at the time. The liver was weighed in each case after taking up excess blood and moisture with a paper towel.

Blocks of tissue for histologic examination were taken from the liver, spleen, kidneys, heart, lungs, stomach, and in many instances, from the colon and suprarenal fixed in 95 per cent alcohol and embedded in paraffin. Sections were stained with hematoxylin eosin and hematoxylin van Gieson, and also with special stains for iron and hemofuscin. Perl's Prussian blue reaction for staining hemosiderin combined with 0.5 per cent basic fuchsin in 50 per cent alcohol, the latter for staining hemofuscin granules, was used extensively. The potassium ferrocyanide and hydrochloric acid solution was used hot as suggested by Abbott. The Nishimura method in which sections are stained for one hour in strong ammonium sulphide and then treated with potassium ferrocyanide and hydrochloric acid was also used. By this method, hemosiderin is stained blue and hemofuscin may be stained deep red by dilute fuchsin. A number of sections were also stained lightly with hematoxylin and then placed in a mixture of one part strong yellow ammonium sulphide and three parts of 95 per cent alcohol for from one to two hours. By this method, hemosiderin is stained intensely black, while nuclei are stained blue and hemofuscin is not stained.

When the experiments had been in progress for about eight months it was decided to make quantitative determinations of the copper in the livers of the remaining animals. After careful study of various methods the one of Rose and Bodansky[24] was chosen as most suitable to our needs. The accuracy of the method was tested by analyzing 6 Gm. of normal rat's liver (three livers previously analyzed showed no copper) to which 25 cc. of the copper standard (0.001 Gm. copper per cubic centimeter) had been added. There was recovered 0.0242 Gm. of copper out of a possible 0.025 Gm. an error of 3.2 per cent. We believe it is safe to assume that the error is not more than 5 per cent in the chemical determinations made by us.

EXPERIMENTAL PIGMENT CIRRHOSIS

EXPERIMENT 1.—*Copper Feeding of Rabbits.*—The report of our experimental results is confined, with a few exceptions, to the thirty-four animals in which chemical determinations were made of the copper in the livers.

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24. Rose, W. C., and Bodansky, Meyer: Biochemical Studies on Marine Organisms, J. Biol. Chem. **44**:104, 1920.

In the first group of seven rabbits, which were given copper acetate in their food for from thirty-three to forty-one weeks, the results on six animals are reported, the data being presented in table 1. It will be seen that in rabbits 1, 2 and 3, relatively large quantities of copper were present in the livers, 116, 100 and 64 mg. respectively per hundred grams of fresh liver tissue. The livers of two control animals taken out of stock were analyzed for copper and both contained only small traces, less than 1 mg. each per hundred gram of liver tissue. It will be seen, therefore, that these three rabbits were able to store in their livers amounts of copper from 100 to 200 times in excess of that normally present.

TABLE 1.—*Copper Feeding of Rabbits*

Rabbit. No.	Duration of Feeding Weeks	Mean Daily Amount Copper Gm.	Total Amount of Copper Fed Gm.	Copper Found per 100 Gm. Liver	Gross Pathology of Liver	Pigment			Histology of Liver	Pathology of other Organs
						Hemofuscin in Liver	Hemosiderin			
							Liver	Spleen		
1	35	0.25	52.56	0.116	Wt. 88 Gm. smooth, soft, greenish	++++	—	+	Slight fibrosis, many pigment phagocytes	Encephalitis?
2	36	0.25	53.81	0.100	Wt. 90 Gm. smooth, dark greenish brown	++++	+	+	Moderate fibrosis, heavy round cell infiltration	—
3	41	0.25	41.37	0.064	Wt. 102 Gm. smooth, greenish brown	+++	—	++	Slight fibrosis	—
4	41	0.25	41.62	0.0165 (loss)	Wt. 108 Gm. smooth, slightly greenish	++	—	++	Slight fibrosis	—
5	33	0.25	52.04	0.026	Wt. 108 Gm. smooth, slightly greenish brown	++	—	++	Bile duct proliferation (coccidial?)	—
6	33	0.25	52.04	0.0042	Wt. 90 Gm. smooth, normal reddish, brown	+	—	..	Slight fibrosis	—

Grossly, five of the six organs varied from a greenish to greenish brown, the color being most marked in the first three animals. The color was probably the result of jaundice, although no bile-plugged capillaries or other evidence of bile-staining could be seen histologically. It is possible that it was also due to the large quantities of hemofuscin pigment. The amount of this pigment in animals 1 and 2 was enormous, as may be seen in figure 1. In the tables the amounts of hemofuscin and hemosiderin are designated by pluses—four plus indicating practically complete filling of the liver cells with pigment, at least those about the peripheries of the lobules; one plus represents small amounts of pigment in a few groups of cells or small amounts diffusely scattered through the lobules; the gradations between these extremes are expressed as two plus and three plus, respectively.

It is most interesting to note how closely the amounts of pigment in the various livers, especially the hemofuscin, parallels the quantities of copper present (table 6). Rabbit 6 likely refused most of the copper poisoned grain as indicated by the small amount of copper found in the liver. It will be noted that a correspondingly small amount of hemofuscin was present and grossly, the liver did not have a greenish cast.

The amount of hemosiderin in the spleen does not hold a constant relationship to the amount of pigment in the liver, or to the quantities of copper found in that organ either in this group or those that follow. This is to be expected in hemochromatosis since the disease is not due to increased blood destruction.

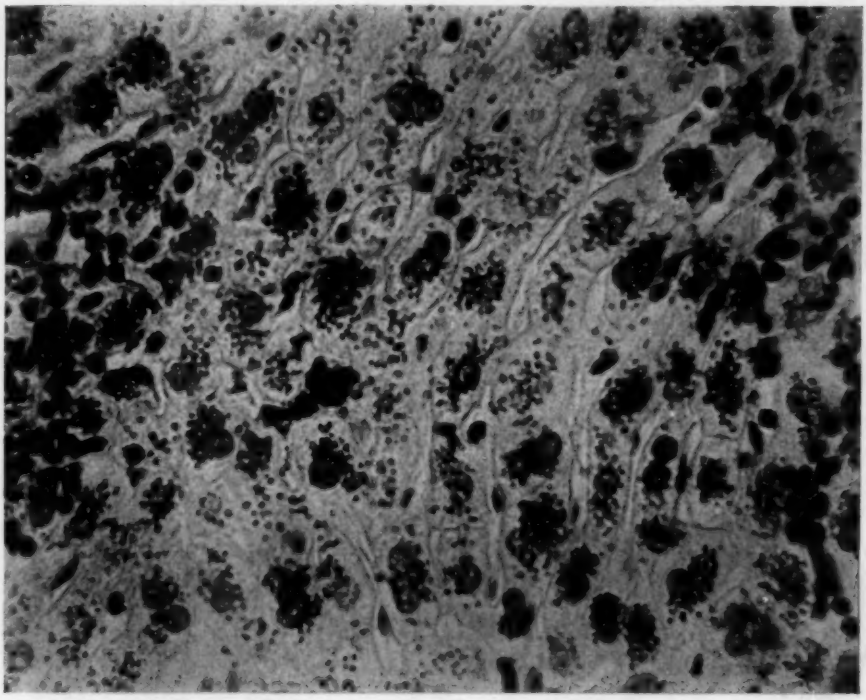

Fig. 1.—Liver of rabbit 2; copper acetate in food for thirty-six weeks. Section shows abundant hemofuscin granules in the liver cells bordering the periportal spaces; × 550. Near the center is a Kupffer cell loaded with hemofuscin; at the edges fibroblasts are beginning to push out among the liver cells. Ammonium sulphide potassium ferrocyanide and fuchsin.

Connective tissue proliferation was not marked in any of the animals, but early fibrosis was found in all except rabbit 5, in which there was considerable bile-duct proliferation, probably due to coccidial infestation. In rabbit 1, a slight increase in fibrous tissue was found about the periportal spaces, and numerous endothelial phagocytes in these areas were loaded with hemofuscin. Rabbit 2 showed a moderate periportal fibrosis with heavy round cell infiltration of the connective tissue (fig. 2). It seemed to us that we might with propriety claim to have produced an early pigment cirrhosis in rabbits 1, 2, 3 and 4. Clinical signs of

encephalitis developed in rabbit 1, but, unfortunately, histologic examination of the brain was not made.

EXPERIMENT 2.—*Copper Feeding and Injection.*—In the second group of seven rabbits that were first given copper in their food, and later subjected to subcutaneous injections, six will be reported, four of which are presented in table 2. Rabbits 8, 9 and 10 were given a mean daily dose of 0.37 Gm. of copper acetate in their food for eleven weeks and then received forty-six, twenty-one and forty-six subcutaneous injections, respectively, of 0.75 cc. of 1 per cent copper acetate over periods of from thirteen to twenty-one weeks. Rabbit 11 was given approximately 0.25 Gm. copper acetate in his food, daily for twenty-four weeks following which ten injections of 1 cc. and five injections of 0.75 cc. of 1 per cent copper acetate

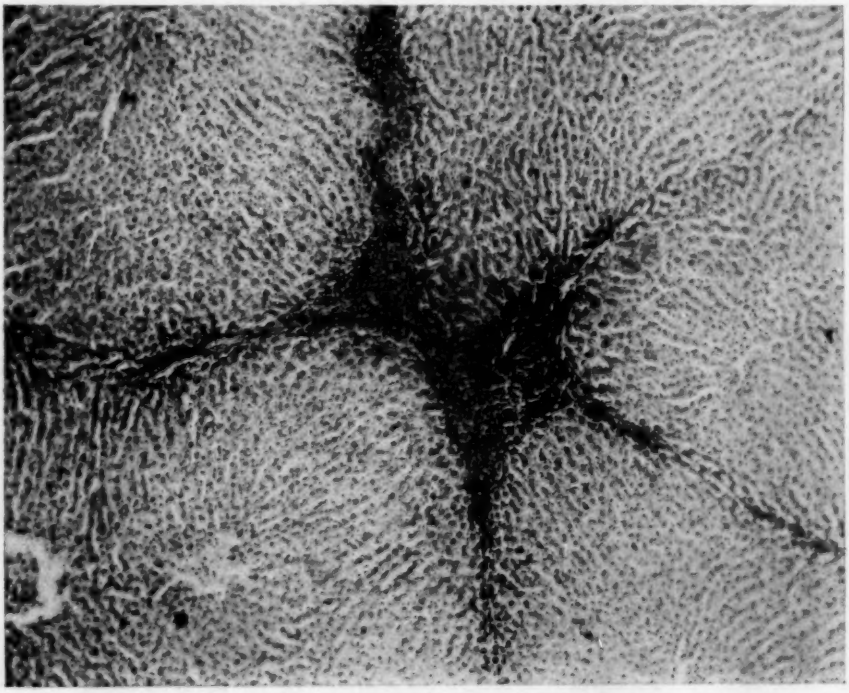

Fig. 2.—Liver of rabbit 2, showing fibrous tissue proliferation in and around the periportal spaces with dense round cell infiltration; × 55. The adjoining liver cells are darkened by the presence of hemofuscin. Hematoxylin and eosin.

solution was administered over a period of fourteen weeks. The animal developed large ulcers at the site of injection so that injections could not be given at regular intervals.

A large amount of copper was stored in the liver of rabbit 8 (137.5 mg. per hundred grams of fresh liver), and moderately large amounts in rabbits 9, 10 and 11 as shown in table 2. The livers in rabbits 8, 9 and 10 were greenish-brown to bluish black. Rabbit 9 had lost a 1 Kg. in weight during the twenty-four weeks of the experiment and his liver was small (60 Gm.). The liver of rabbit 11 showed grossly some evidence of fibrosis in the form of roughening along the edges. Microscopically, the connective tissue proliferation was marked, some of the

lobules being completely outlined with connective tissue while in the periportal connective tissue there was marked round cell infiltration (fig. 5). In the other three animals, there was a slight fibrosis of approximately the same grade as in the first group.

The large amounts of hemofuscin in the livers of the four animals closely paralleled the quantities of copper found much as in the first group (table 6). In rabbit 9, numerous endothelial phagocytes were found packed with hemofuscin granules (fig. 3), while in rabbit 8, many of the phagocytic cells had fused to form large multinuclear giant cells (fig. 4). In rabbit 9, the malpighian bodies of the spleen were well infiltrated with amyloid.

All four animals showed an early pigment cirrhosis.

TABLE 2.—*Copper Feeding and Infections*

Rabbit No.	Total Duration of Experiment, Weeks	Duration of Copper Feeding Weeks	No. of Injections	Total Copper		Copper Found per 100 Gm. Liver	Gross pathology of Liver	Pigment			Histology of Liver	Pathology of Other Organs
				Fed. Gm.	Injected			Hemofuscin in Liver	Hemosiderin Liver	Hemosiderin Spleen		
8	32	11	46	19.8	.322	0.1375	Wt. 96 Gm. smooth, greenish brown	++++	—	++	Slight fibrosis, many pigment phagocytes and giant cells	—
9	24	11	21	19.8	.075	0.056	Wt. 60 Gm. smooth, bluish black	++++	—	++++	Slight fibrosis, many pigment phagocytes, a few giant cells	Beginning pneumonia, amyloid spleen
10	30	11	46	19.8	.322	0.070	Wt. 90 Gm. smooth, greenish brown	+++	—	+++	Very slight fibrosis	Marked eczema ears
11	38	24	15	31.2	.147	0.041	Wt. 94 Gm. slightly roughened along edges	++	—	tr.	Marked fibrosis	Ulceration at site of injection

Two tan female rabbits, 13 and 14, were given mean daily doses of 0.12 Gm. each of copper acetate for sixteen weeks. They were given small amounts because they ate the poisoned grain poorly. At the end of sixteen weeks, each animal was purposely given a large dose of copper acetate subcutaneously (5 cc. of 1 per cent solution). Both animals died in about twenty-four hours. In rabbit 13, there was edema and congestion of the subcutaneous tissues at the site of injection and marked congestion of the lungs. The liver was large, weighing 164 Gm. The surface was smooth with yellowish-brown areas and a number of small subcapsular hemorrhages. The cut surface revealed mushy brick red tissue that was so soft that some of the material ran out when the liver was sectioned. Microscopically, there was early necrosis of the central parts of the lobules in places involving the entire lobule. The nuclei were pyknotic or pale and the liver cells were separated from one another. In a few places the lobules were fairly well preserved. There was a fairly-well marked fibrous tissue reaction about the periportal spaces and marked round cell infiltration. Perl's prussian blue reaction

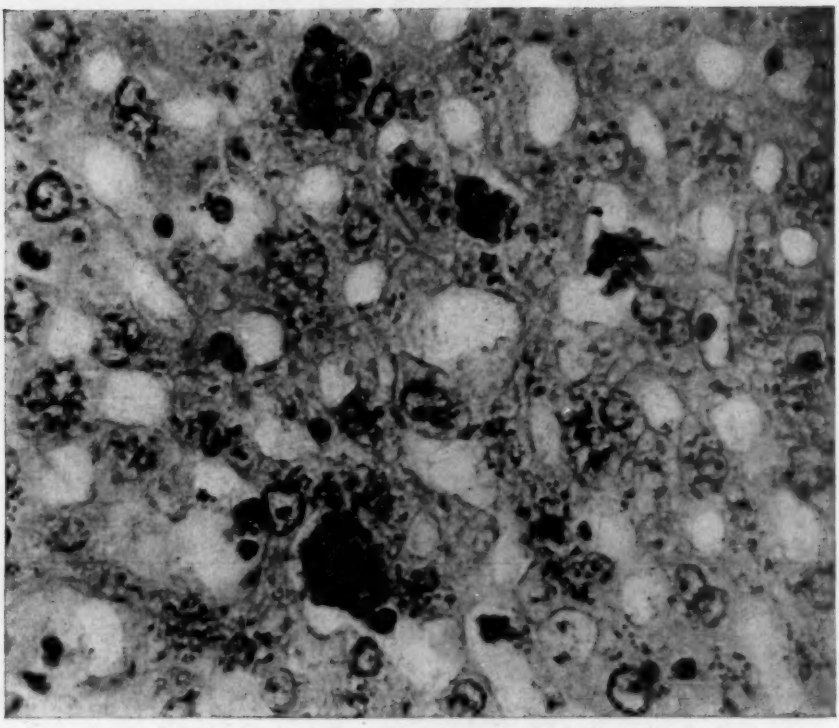

Fig. 3.—Liver of rabbit 9; copper acetate in food for eleven weeks followed by subcutaneous injections for thirteen weeks. Section shows several large phagocytic cells filled with hemofuscin; × 730. The surrounding liver cells contain a moderate amount of pigment. Ammonium sulphide, potassium ferrocyanide and fuchsin.

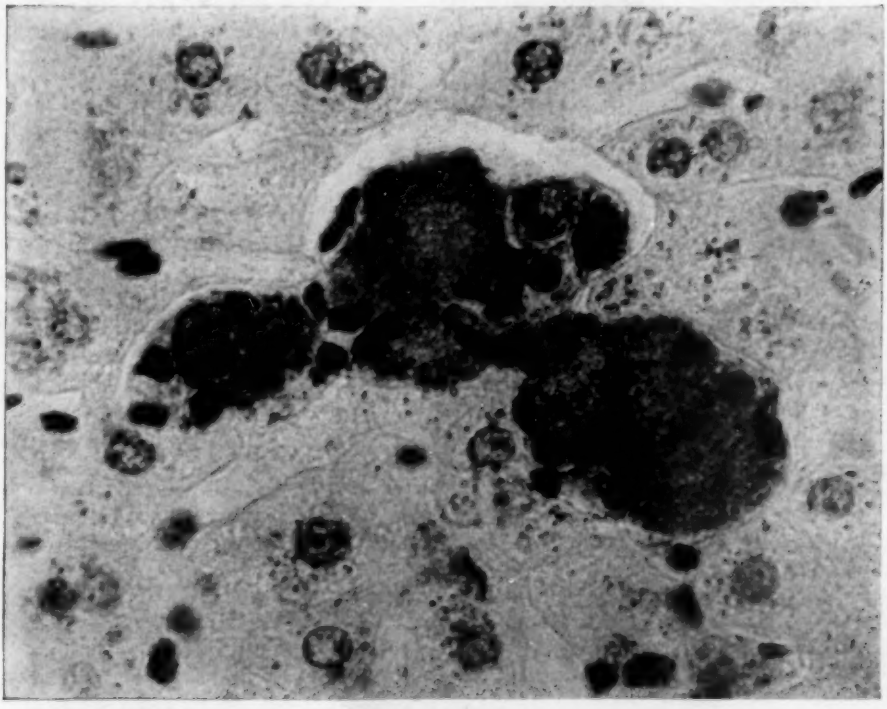

Fig. 4.—Liver of rabbit 8; copper acetate in food for eleven weeks followed by subcutaneous injections of copper salts for twenty-one weeks. Section shows a group of large multinuclear giant cells which contain considerable pigment; × 860. Ammonium sulphide, potassium ferrocyanide and fuchsin.

failed to show hemosiderin, but a large number of hemofuscin granules had stained with basic fuchsin in the cells of the peripheries of the lobules where the liver cells were somewhat better preserved than at the centers.

The kidneys showed granular swelling of the tubular epithelium with much blood and many blood casts in the tubules. Lesions were not found in the glomeruli.

Rabbit 14 showed little or no congestion of the lungs. The liver was smaller than the one just described, weighing only 100 Gm., but showing even more extensive necrosis on histologic examination. There was practically the same amount of periportal fibrosis and round cell infiltration. Numerous hemofuscin granules appeared in the liver cells of the peripheries of the lobules. The Berlin blue reaction showed considerable blue-staining granular material in the venous

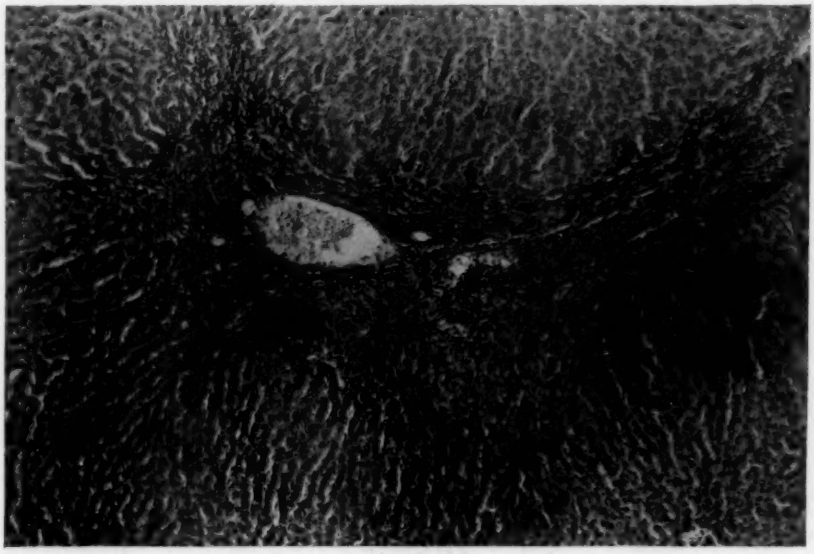

Fig. 5.—Liver of rabbit 11; copper acetate in food for twenty-four weeks followed by subcutaneous injections of copper salts for fourteen weeks. Section shows marked increase in the periportal connective tissue; × 85. Hematoxylin and eosin.

sinuses. Grossly, the blood was thin and watery. Chemical determination of copper were not made on the livers in these rabbits.

They showed an early pigment cirrhosis associated with necrosis of the liver due to acute copper poisoning.

EXPERIMENT 3.—*Injections of Copper.*—This group consisted of five rabbits which were given subcutaneous injections of 1 per cent copper acetate solution over periods varying from one to ten weeks. Only four animals are reported (table 3) since in one, copper determination was not made. Rabbits 15 and 16 were given each a total of 0.07 Gm. of copper acetate in the course of a week. Rabbit 15 died following the third and rabbit 16, following the fourth injection. Both animals showed edema and congestion of the subcutaneous tissues at the site of injection and marked congestion of the lungs. In both, the livers were pale yellow, opaque, soft and friable, evidently undergoing necrosis. Microscopically,

there was some increase in the periportal connective tissue with moderate bile-duct proliferation, probably due to coccidial infestation. There was a zone of early necrosis about the periportal spaces which involved about half of each lobule. The cells in these areas had lost their nuclear staining, the cytoplasm stained brick red with eosin, and polymorphonuclear leukocytes were present in moderate numbers about the borders of the necrotic areas.

Quantitative estimations of copper showed that practically equal amounts of the metal had been stored in the two livers, viz., 11 mg. per hundred grams of liver in rabbit 15 and 10 mg. in rabbit 16. Since each animal received the same quantity of copper acetate solution it is possible to estimate the percentage of pure copper stored in each liver. Rabbit 15 stored 0.0092 Gm. in the whole liver or 42 per cent and rabbit 16 stored 0.0072 Gm., or 31 per cent of the copper given.

The amount of hemofuscin was small as one would expect from the injection of such small quantities of copper over a period of only one week. These results

TABLE 3.—*Injections of Copper*

Rabbit No.	Duration of Experiment Weeks	No. of Injections	Total Amount of Copper Injected Gm.	Copper Found in 100 Gm. Liver	Gross Pathology of Liver	Pigments			Histology of Liver	Pathology in Other Organs
						Hemofuscin in Liver	Hemosiderin			
							Liver	Spleen		
15	1	3	0.07	0.011	Wt. 84 Gm. yellow, opaque friable	+	—	+	Slight fibrosis, necrosis about periportal spaces	Congestion and edema of lungs
16	1	4	0.07	0.010	Wt. 72 Gm. yellow, opaque, friable	++	—	—	Slight fibrosis, areas of necrosis	Cloudy swelling kidneys, inflammation at site of injection, congestion and edema of lungs
17	4	6	0.13	0.069	Wt. 70 Gm. yellow, opaque, soft, friable	+	++	+	Slight fibrosis, early necrosis	Congestion and edema of lungs, hemosiderin in kidneys
18	10	21	0.307	0.013	Wt. 55 Gm. smooth, dark reddish brown	++	—	++	Slight fibrosis, areas of necrosis	Marked emaciation, large ulcer at site of injection

demonstrate the early lesions found in cases of acute copper poisoning and show the marked capacity of the liver to store copper.

EXPERIMENT 4.—*Alcohol and Copper.*—In this experiment rabbits and white rats were given a mixture of alcohol and copper by stomach tube. Fourteen rabbits were used, but only four survived long enough to be of value. Twenty white rats were also treated in this way, but the results of only six are reported, since in this number quantitative copper determinations were made.

Rabbits weighing from 2,000 to 3,000 Gm. were selected and five times a week were given 20 cc. of a mixture consisting of four parts of 50 per cent alcohol and one part of 5 per cent copper acetate solution. This represents 0.2 Gm. of copper acetate per dose. A no. 22 rubber catheter, which is too large to readily pass through the larynx, was used as a stomach tube. The tube was washed out with water following each gavage. Somewhat smaller doses were given for the first week or ten days in order to accustom the animals to the treatment. The animals were treated early in the morning before feeding in the hope of putting the

mixture of alcohol and copper into an empty stomach. No food was given until afternoon. Food left in the stomach from the day before often defeated this ideal of an empty stomach, and no doubt resulted indirectly in the death of a number of animals due to the mixture of alcohol and copper being forced back up the esophagus and into the trachea and lungs. A full dose of 20 cc. of the mixture of alcohol and copper on an empty stomach caused intoxication lasting from one to two hours in at least some of the animals, others became only drowsy with markedly increased respiration.

Grossly, the livers of the four animals were nearer the normal than in any of the preceding experiments. In rabbit 21, the liver was decidedly small (55 Gm.) and dark brown. In rabbit 23, the liver was large (122 Gm.) and smooth with some yellowish coloring about the edges.

The results of this experiment are illuminating in view of Mallory's[25] contention that alcohol hastens and aggravates the effects of copper in producing hemochromatosis. Chemical analyses of the livers of the four rabbits (20, 21, 22 and 23) show practically equal, but relatively small, amounts of copper present. Rabbit 20 was gavaged for fourteen weeks in which time he was given 564 cc. of 50 per cent alcohol and 7.05 Gm. of copper acetate. Only 17 mg. of copper per hundred grains of liver had accumulated in the organ during that time (table 4). Rabbits 21, 22 and 23 were gavaged for twenty, thirty-two and thirty-two weeks respectively, and received correspondingly larger total doses of alcohol and copper. These animals were able to store in their livers only 11, 16 and 11 mg. of copper, respectively. Rabbits 22 and 23 received 21.4 and 24.2 Gm. of copper acetate respectively, amounts in excess of that given rabbit 8 (table 2), who was able to store 137 mg. of copper in the liver. Rabbit 8 was given about 20 Gm. of copper salt, but probably ingested only a fraction of that amount. Expressed in percentage rabbit 20 stored in the liver approximately 0.7 per cent of the copper administered while the other three rabbits stored 0.2 per cent or less. These low percentages indicate that alcohol not only does not increase the storage of copper in the liver, but actually inhibits it.

In accord with what has been said previously, hemofuscin was found in only moderate amounts as shown in tables 4 and 6. In animals 21 and 22 the amount of hemofuscin was somewhat greater than would be expected considering the small quantities of copper stored. The rabbit (23) that was fed the largest amounts of alcohol and copper, had only a small quantity of hemofuscin in the liver.

The hemosiderin in the spleen was variable as in the other groups and did not show a constant relationship to the experimental procedure. The connective tissue changes in the liver were similar to those seen in the preceding experiments. The fibrosis in these cases might have been due in part to the effects of the alcohol.

Three of the animals (21, 22 and 23) developed bronchopneumonia toward the end accompanied by abscess formation, while animal 21 had in addition an acute enteritis. Animal 20 showed clinical signs of encephalitis, but this was not investigated histologically.

The twenty white rats which were gavaged for from twenty-two to fifty-four months with from 3.5 to 4 cc. of the mixture of alcohol and copper had normal livers as far as could be determined by inspection. Rats 1, 2 and 3 each received a total of 577 cc. of 50 per cent alcohol and 7.5 Gm. of copper acetate. Estimating a rat at about one tenth the weight of a rabbit it will be seen that the dosage in the rats is considerably higher in proportion to their weights than in the rabbits. The

25. Mallory, F. B.: Hemochromatosis and Chronic Poisoning with Copper, Arch. Int. Med. **37**:336 (March) 1926.

greater number of white rats were intoxicated for from one to three hours following the morning gavage, yet a number of these animals withstood this treatment with comparatively slight ill effects for a year.

Rats 11 to 20 were given each a mean dose of 0.018 Gm. of copper mixed with their feed daily for twenty-three weeks. It was then decided to put them on the mixture of alcohol and copper and for twenty-two weeks they received 4 cc. of this mixture daily by stomach tube. In table 4, the figure 2.48 Gm. represents

TABLE 4.—*Alcohol and Copper by Stomach Tube*

No. of Animal (Rabbits)	Duration of Experiment Weeks	Daily Amount Alcohol and Copper Mixture Cc.	Total Quantity		Copper Found per 100 Gm. Liver	Gross Pathology Liver	Pigments			Histology of Liver	Pathology of Other Organs
			50 Per Cent Alcohol Given, Cc.	Copper Acetate Given, Gm.			Hemofuscin in Liver	Hemosiderin			
								Liver	Spleen		
20	14	20	564	7.05	0.017	Wt. 104 Gm. few grayish patches, otherwise normal	++	—	+	Slight periportal fibrosis	Encephalitis?
21	20	20	980	12.2	0.011	Wt. 55 Gm. smooth, normal appearance	++	+	++++	Moderate periportal fibrosis	Bronchopneumonia, enteritis
22	32	20	1552	21.4	0.016	Wt. 96 Gm. normal appearance	+++	—	tr.	Slight periportal fibrosis	Slight bronchopneumonia
23	32	20	1936	24.2	0.011	Wt. 122 Gm. large, smooth, yellow along edges	+	—	—	Slight periportal fibrosis	Bronchopneumonia with abscesses
(White Rats)											
1	54	3.5	577	7.5	0.001	Wt. 12 Gm. smooth, congested centers	—	—	+	Slight fatty infiltration, no fibrosis	Congestion and edema of lungs, absence of gallbladder
2	41	3.5	577	7.5	tr.	Wt. 11 Gm. normal	—	—	—	Normal	
3	41	3.5	577	7.5	tr.	Wt. 16.25 Gm. congested	—	—	—	Normal	
11	22	4	350	2.48 5.32	0.0018	Wt. 15.85 Gm. congested	tr.	—	+	Normal	Congestion and edema of lungs
12	22	4	350	2.48 5.32	tr.	Wt. 11.7 Gm. normal	+	—	+	Normal	Slight chronic pneumonia
13	22	4	350	2.48 5.32	tr.	Wt. 14 Gm. normal	+	—	—	Slight fibrosis, few granulomatous nodules	Moderate chronic pneumonia

copper acetate given in the food; the lower figure, 5.32 Gm., represents copper acetate administered with the alcohol.

White rats apparently absorb copper from the gastro-intestinal tract poorly, especially when mixed with alcohol. Analyses of the livers in six animals showed such small quantities of copper that accurate determinations could not be made. Using the whole liver, except the small blocks removed for histologic study, gave only from 10 to 15 Gm. of material for analysis. None of the animals stored more than from 1 to 2 mg. of copper per hundred grams of liver tissue. This represents only from 0.1 to 0.2 mg. of copper in the samples analyzed,

amounts too small to be accurately measured by our methods. We must conclude, therefore, that white rats fed the mixture of alcohol and copper for from ten to twelve months stored only traces of copper in their livers. The livers of three normal rats analyzed in one lot did not show any copper.

Likewise, only two of the six rats showed any hemofuscin and in these the pigment was found in only a few scattered groups of liver cells. Hemosiderin was not present in any of the rats, and only one showed fibrosis and that was in connection with a chronic granulomatous process in which small tubercle-like nodules were produced in the liver.

EXPERIMENT 5.—*White Rats Fed Copper Acetate.*—Thirty-eight white rats were given from 0.018 to 0.04 Gm. of copper acetate daily mixed with the balanced diet over a period of forty-two weeks. Out of this group eight livers were analyzed for copper and histologic studies made on the various organs. Results of the chemical studies show that only small quantities of copper were stored in the livers. In five of the animals, as may be seen in table 5, the copper content was decidedly greater than in the animals that received alcohol. Rats 51 and 54 were young vigorous animals at the beginning of the experiment and ate much larger quantities of the copper-poisoned food than did the older animals. These animals stored approximately 11 mg. of copper per hundred grams of liver tissue.

Six rats from the same group as rats 51 and 54 at the end of the eighteenth week of feeding were splenectomized and then fed copper in the amount of 0.04 Gm. daily for twenty-four weeks. This was done to determine what effect, if any, removal of the spleen would have on storage of pigment in the liver. Only traces of copper were found in the livers of rats 46 and 47 in amounts too small to measure accurately.

Hemofuscin pigment, while small in amount, was definitely increased as compared with the rats that received alcohol (table 6). Hemofuscin was absent in only one rat in the present group, while one of them (54) had a relatively high copper content in the liver and also had a moderate amount of hemofuscin. Three contained traces of hemosiderin in the Kupffer cells and in the connective tissue. All but one of the animals showed a slight connective tissue proliferation about the periportal spaces and beginning degeneration and necrosis of the liver cells in these areas.

The spleen in most of this group contained considerable amounts of hemosiderin. Several animals had more or less chronic pneumonia and the last three animals listed in table 5 showed hemofuscin in scattered groups of kidney tubules and hemosiderin in small quantities in the reticulo-endothelial cells of the kidney. Splenectomy had been performed on two of the animals.

While we can scarcely claim to have produced a pigment cirrhosis in this group of white rats, yet it is evident that the changes produced tended in that direction. Furthermore, the amounts of copper, hemofuscin and fibrosis in the livers of this group were definitely greater than in animals given alcohol and copper, in spite of the fact that one group of the latter was treated for ten weeks longer than those of group 5. This study also illustrates the great tolerance of the white rat for substances that ordinarily produce hepatic damage.

EXPERIMENT 6.—*Injections of Copper in Sheep.*—Two sheep, wethers, from 6 to 8 months old, weighing 80 and 90 pounds respectively, were obtained when this study had been in progress for six to eight months. We were not convinced at that time, since no chemical analyses had been made, that the copper salt was being absorbed from the intestine of our experimental animals. It was decided therefore to treat these animals with subcutaneous injections of copper

TABLE 5.—*Copper Feeding of Rats*

Rat Number	Duration of Experiment, Weeks	Mean Daily Feeding Cu. Acetate Fed Gm.	Total Amount Cu. Acetate Fed Gm.	Copper Found per 100 Gm. Liver Gm.	Gross Pathology Liver	Pigments			Histology of Liver	Pathology of Other Organs
						Hemosiderin				
						Hemofuscin in Liver	Liver	Spleen		
31	42	0.018	4.75	none	Wt. 15.6 Gm. normal	+	—	+++	Areas of parenchymatous degeneration	—
37	42	0.018	4.75	0.0021	Wt. 12.5 Gm. congested	+	tr.	++	Swelling of cells, early necrosis, slight fibrosis	Large abscess of left lung
38	42	0.018	4.75	0.0021	Wt. 13 Gm. congested	—	—	+++	Moderate swelling of liver cells	Some chronic pneumonia, parenchymatous degeneration of kidney
51	43	0.027	7.02	0.011	Wt. 8.85 Gm. normal	+	—	+	Slight fibrosis	Some chronic pneumonia
54	43	0.027	7.02	0.011	Wt. 8 Gm. normal	++	—	—	Some granular swelling liver cells, slight fibrosis	—
66	42	0.025	6.42	0.0035	Wt. 9 Gm. normal	+	tr.	+++	—	Parenchymatous degeneration of kidney, hemofuscin in tubular epithelium, hemosiderin in endothelial cells
46	42	0.018 0.04	7.8	tr.	Wt. 9 Gm. congested	tr.	tr.	.....	Slight fibrosis	Splenectomy eighteenth wk., slight chronic pneumonia, some hemofuscin and hemosiderin in kidney
47	42	0.018 0.04	7.8	tr.	Wt. 10.9 Gm. normal	tr.	—	.....	Some granular swelling liver cells, slight fibrosis	Splenectomy eighteenth wk., parenchymatous degeneration of kidneys, considerable hemofuscin, trace hemosiderin in tubular epithelium

acetate solution. Two, and later, three times per week they were given about 2.5 cc. of 1 per cent copper acetate, diluted up to 10 cc. with distilled water immediately before injection. These small doses were given because Mallory [25] had stated that sheep are sensitive to copper and tolerate actual doses about equal to those given to rabbits. We were also anxious to avoid abscess formation with ulceration and infection. When given this small amount of copper, the animals failed to gain weight in spite of a sunny, well-ventilated pen with plenty of feed.

Autopsy Protocol of Sheep 1.—The autopsy revealed some slight inflammation at the sites of injection, but no abscess formation. The heart and lungs were normal. The liver appeared small and firm and weighed 416 Gm. The surface was smooth and a peculiar light brown. The cut surface was the same color. Definite fibrosis could not be distinguished grossly. The spleen seemed rather large (72 Gm.), the capsule was thickened and the pulp had a dark, reddish-brown appearance. The trabeculae were prominent, while the pulp was somewhat soft.

TABLE 6.—*Relation of Copper Content to Hemofuscin*

Rabbit No.	Copper in Liver Mg.	Hemofuscin in Liver
1	116	++++
2	100	++++
3	64	+++
5	26	++
6	4	+
8	137	++++
9	56	++++
10	70	+++
11	41	++
20	17	++
21	11	++
22	16	+++
23	11	+
Rat No.		
1	1	—
2	tr	—
3	tr	—
37	2	+
28	2	—
51	11	+
54	11	++
66	3.5	+

The kidneys were also distinctly brownish. The pancreas, stomach and intestine were grossly normal.

Histologic examination of the liver revealed a moderate but definite early fibrous tissue reaction about practically all of the periportal spaces (fig. 6). Some of the liver cells adjoining the periportal spaces showed degeneration and necrosis. In some, the cytoplasm was granular and the cells were considerably swollen; in others, the cytoplasm was coarsely vacuolate and the nuclei, pale-staining or pyknotic. Other cells were hyaline and the nuclei had disappeared. Swollen von Kupffer cells showing the same degenerative changes occurred in capillary spaces throughout the lobules. Polymorphonuclear leukocytes surrounded many of the damaged and necrotic von Kupffer cells. There was a moderately dense cellular infiltration of the periportal spaces, composed partly of polymorphonuclear leukocytes and partly of round cells.

Perl's prussian blue stain did not show hemosiderin in the liver. The degenerating von Kupffer cells stained heavily with basic fuchsin, but hemofuscin granules could not be made out. The spleen contained a large amount of hemosiderin scattered through the pulp.

The kidneys showed marked granular swelling of the tubular epithelium with degeneration and beginning necrosis. There were a number of granular and

hyaline casts. A few blood casts appeared in the convoluted tubules while many large blood casts were seen in the collecting tubules. The glomeruli showed little change, except for some coagulated fluid in Bowman's space.

Perl's reaction and Nishimura's stain showed numerous granules of hemosiderin diffusely distributed in the convoluted tubules and smaller amounts in the ascending limbs of Henle's loop. In some of the tubules much blue-staining granular material was seen in the lumina. Hemofuscin was not found.

The pancreas was normal and pigment was not seen.

Autopsy of Sheep 2.—Lesions were found similar to those in sheep 1. The liver had the same appearance and consistency and weighed 425 Gm. The spleen and kidneys were grossly the same as in sheep 1.

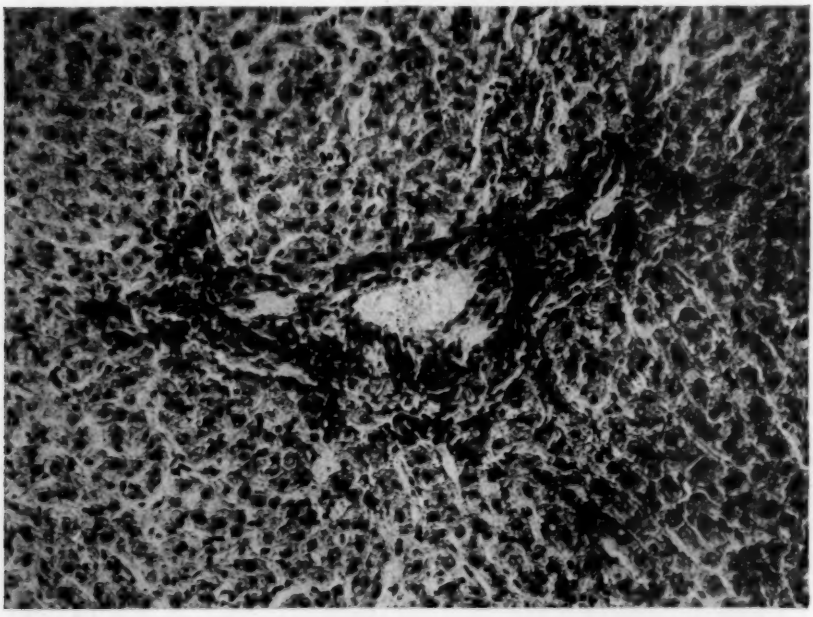

Fig. 6.—Liver of sheep *2*; copper acetate subcutaneously for six months. Section shows beginning fibrosis in and around the periportal spaces; × 225. Hematoxylin and van Gieson.

Histologic examination showed slightly more necrosis of the liver cells than in the other animal. The spleen was even more abundantly loaded with hemosiderin. The kidneys showed a well marked early necrosis of the tubular epithelium somewhat more than in sheep 1, but no hemofuscin or hemosiderin in the tubules. Definite casts were not seen.

The heart revealed some beginning degeneration of small groups of muscle cells, usually near the vessels. The degenerating cells were swollen, slightly granular or hyaline, but pigment was not seen. There was a slight perivascular round cell infiltration.

Each animal received 1.4 Gm. of copper acetate; calculated as pure copper, this equals 0.446 Gm. The chemical analysis of the livers, revealed 0.058 Gm. in sheep 1, and in the second animal, 0.0577 Gm. of copper per hundred grams of liver tissue. These amounts represent 54.3 per cent and 54.9 per cent of the total

copper administered stored in the livers of these animals. The actual amounts of copper stored in the whole liver of sheep 1 equals 0.2413 Gm., in sheep 2, 0.2452 Gm. Although the actual amount of copper is small yet since more than 54 per cent of the total quantity was stored in the livers we may assume that the early necrosis of the liver cells and the beginning fibrosis are actually the result of the presence of copper. This assumption is strengthened by the fact that the lesion in both livers were practically identical in kind and severity.

The absence of pigment in the liver is difficult to explain. The excess amounts of hemosiderin in the spleens and in the kidneys of one animal indicate an hemolytic action on the red blood cells. Unfortunately, blood counts were not made.

EXPERIMENT 7.—*Distribution of Copper in Other Organs.*—When it was found that relatively large amounts of copper were stored in the liver in animals fed or injected with copper acetate, the question arose as to whether any copper was stored in other organs than the liver, and if so, in what amounts. We expected that the walls of the stomach, small intestines and especially the colon would contain more or less copper. The presence of copper in the kidneys was considered doubtful as little, if any, copper is eliminated in the urine.

Rabbit 3 which had been fed copper acetate daily for forty-one weeks was selected for the experiment. Analysis of 20 Gm. of liver tissue showed 0.0643 Gm. of copper per hundred grams of liver substance. The stomach was washed free of food and copper, the final washings being made with distilled water. After taking up the excess moisture with blotting paper 35 Gm. of fresh tissue was cut into small pieces and digested with strong acids. The small intestine and colon were treated in like manner. Kidney tissue to the amount of 18 Gm. was digested and analyzed. The following results were obtained from the determination: A trace of copper was found in the small intestine, a faint trace in the stomach, while no copper could be demonstrated in the colon or kidneys.

This experiment clearly illustrates the specificity of the liver in the storage of copper, and makes it likely at least, that liver damage may be at times the result of chronic poisoning with copper.

COMMENT

Early Lesion of Hemochromatosis.—The early lesion of pigment cirrhosis is well shown in the experimental lesions produced in rabbits poisoned with copper. The first effect seems to be the accumulation of hemofuscin granules in the Kuppfer cells, liver cells and periportal connective tissue. The hepatic cells in the vicinity of the portal spaces after from six to ten months of feeding contain large amounts of pigment. The Kuppfer cells swell considerably as the pigment accumulates in them, round up, become detached and tend to migrate along the sinusoids to the periportal spaces. As can be seen in fig. 3, some of the phagocytic cells become greatly enlarged and completely filled with hemofuscin granules. Indeed some of the cells fuse to form pigment-ladened-giant cells (fig. 4). Apparently some of the liver cells succumb as they become loaded with pigment, while at the same time, the presence of the pigment about the periportal spaces stimulates connective tissue growth causing a moderate fibrosis (figs. 1, 2 and 5).

In human hemochromatosis, the hemofuscin gradually gives place to hemosiderin, and this pigment increases greatly in amount with a cor-

responding increase in connective tissue until in the course of years a well-developed pigment cirrhosis is established.

Hemofuscin—the First Pigment Formed.—The two pigments of hemochromatosis have been variously interpreted by different investigators in regard to their composition and sequence of appearance in the tissues. Von Recklinghausen thought both pigments were derived from hemoglobin, hemosiderin coming from the red cells, while hemofucsin was considered to be a condensation material brought to the cells in solution.

M. B. Schmidt [26] believes that hemosiderin is the first pigment formed, that in the earlier stages the pigment reacts for iron, and that later, the iron reaction disappears as hemofuscin develops. The experimental lesions in both rabbits and white rats demonstrate clearly that hemofuscin is the first pigment to appear and that it becomes extremely abundant before any hemosiderin can be demonstrated. Mallory [1] has pointed out that hemofuscin is the earlier pigment, and he has suggested that hemofuscin becomes transformed into hemosiderin, at least in some species, e.g., monkeys and man. He believes that the rabbit liver is unable to convert hemofuscin into iron-reacting hemosiderin.

Whether hemofuscin is converted into hemosiderin as Mallory supposes, is a question difficult of proof. It is true that hemofuscin appears in the Kupffer and liver cells of rabbits within a few weeks or months after the beginning of copper poisoning. It is also true that granules of hemosiderin appear later in these same liver cells in some species. In two of our rabbits, 7 and 21, granules of hemofuscin and hemosiderin appear side by side in the same liver cells, the hemosiderin granules staining blue with potassium ferrocyanide and hydrochloric acid, the hemofuscin granules staining red with basic fuchsin. Although we believe, for reasons that appear later, that hemofuscin is converted into hemosiderin, yet the mere presence of the two pigments in the same cell does not prove that one is derived from the other. It is possible that the two pigments are different chemical derivatives of hemoglobin.

Nature of Hemofuscin.—The first step in the solution of the foregoing question is obviously to determine whether or not hemofuscin contains iron. Many authors, including von Recklinghausen,[5] believe that hemofuscin contains iron in a bound form and therefore difficult of demonstration. Abbott [13] found that the iron-reacting pigment in her case of hemochromatosis reacted unevenly to Perl's test. Granules that showed only a light yellowish green at the end of twenty minutes in cold hydrochloric acid stained at once a deep blue color on being placed in

26. Schmidt, M. B.: Ueber die Verwandtschaft der Hämatogenen und autochthonen Pigmente und deren Stellung zum sogenannten Hämosiderin, Virchows Arch. f. path. Anat. **115**:397, 1889.

hot acid. She concludes that all the granules, both the darker brown and the paler yellow in the liver, lymph nodes, and pancreas, are iron-containing, the essential difference being that in one the iron is in ionic form while in the other it is firmly bound. Abbott calls the paler granules hemofuscin, the darker granules, hemosiderin. Rosenfeld [27] claimed to have isolated hemofuscin which he analyzed chemically. He reported 3.7 per cent sulphur, but no iron, and therefore concluded that hemofuscin belonged to the melanins. Wells [28] stated that hemofuscin is a name given to several different pigments which resemble one another in that they do not contain iron. There is little doubt that several chemically different pigments have been included under the name hemofuscin by different authors. Rosenfeld was probably working with a melanin, but certainly not with the pigment found in copper-poisoned rabbits.

The pigment of copper poisoning which resembles closely the hemofuscin of hemochromatosis and which may be identical with it, can be shown conclusively to contain iron. We have been able to stain the hemofuscin granules blue with potassium ferrocyanide and hydrochloric acid after properly treating the sections to oxidize the bound iron to ionic form. The experimental data will shortly be published by one of us (E. M. H.). When we speak of hemofuscin, we refer to the pigment which ordinarily fails to stain blue even with hot hydrochloric acid and potassium ferrocyanide. After treating sections with hot potassium ferrocyanide and hydrochloric acid mixture they were stained for twenty minutes in 0.5 per cent basic fuchsin in 50 per cent alcohol. The granules which fail to stain blue but, on the other hand, stain red with fuchsin are regarded as hemofuscin.

If we accept the fact that hemofuscin contains iron in bound form we strengthen materially the probability that hemosiderin is derived from hemofuscin. This fact also adds weight to the evidence which has accumulated over a period of years in favor of hemoglobin as the source of both pigments.

Mallory [1] also advanced the theory that copper stored in the liver during the course of copper feeding is probably present in the hemofuscin granules in combination with iron. Kobert [23] referred to the readiness with which iron of hemoglobin combines with copper. He stated that if a solution of hemoglobin is mixed with a weak solution of a copper salt the hemoglobin is precipitated as a cuprohemol compound. The dried compound is used therapeutically as a nonpoisonous copper preparation.

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27. Quoted from Wells: Chem. Path., 1925, p. 544.

28. Wells, H. G.: Hemofuscin, Chem. Path., 1925, p. 544.

We have shown by chemical analysis the presence of relatively large quantities of copper in the livers of rabbits fed on copper. It has further been shown that hemofuscin contains iron. We have also shown that some relationship apparently exists between the quantity of copper in the liver tissue and the amount of hemofuscin. In table 6 a fairly close parallel is shown between the two. This may be interpreted as meaning that the copper is actually present in the hemofuscin or, on the other hand, it may mean that increased amounts of copper cause greater damage to liver cells with increased interference with metabolism of iron. Hemofuscin may be the expression, therefore, of the upset in iron metabolism which is roughly proportional to the amount of copper in the liver. In the light of Kobert's statement and in view of the parallelism shown to exist between the quantities of hemofuscin and copper, it is at least reasonable to suppose, as Mallory does, that copper as well as iron is present in the hemofuscin granules.

Working on this hypothesis, we have attempted to demonstrate the presence of copper in this pigment by means of microchemical tests, but so far without success. Notwithstanding this, we are inclined to believe that copper is stored in the liver in the hemofuscin granules. Perhaps when the proper microchemical test is applied, its presence will be demonstrated. This subject will be further elaborated in a later paper.

Metabolism of Iron.—An adult man of from 60 to 70 Kg. in weight has approximately 3 Gm. of iron in his body, of which 2.5 Gm. are found in the hemoglobin. In hemochromatosis, the liver alone often contains 30 Gm. of iron. Since it has been shown that increased blood destruction is not responsible for this great excess of iron, the question naturally arises—What is the genesis of the iron in this disease? In 1900, Meltzer [18] was the first to suggest that there might be a perverted iron metabolism in hemochromatosis, and that by some fault in its mechanism, the organs and cells of the body retain most of the iron which reaches them in the normal round of the blood stream. Parker,[19] also Gaskell [20] and his associates, support this theory presented by Meltzer.[18] In 1917, Howard and Stevens [4] found in a case of hemochromatosis in which anemia was not present (the hemoglobin reading was 100 per cent), that the iron eliminated in the urine and feces was slightly less than the iron contained in the food. McClure,[21] a year later, also conducted an experiment on the iron metabolism of a patient suffering from hemochromatosis. When the amount of iron in the diet and that excreted in the urine and feces had been determined he found that 20 per cent of the ingested iron had been retained. The patient had ingested 240 mg. and had excreted 192 mg. The experimental data, therefore, are consistent with the hypothesis that there is an abnormal retention of iron in hemochromatosis.

In rabbits poisoned with copper, it seems likely that copper damages the liver cells and thus interferes with their power to properly work over the hemoglobin derivatives so that iron is retained and accumulates in the tissues in granular form as hemofuscin. As stated before, it may be that copper salts which are present in the liver cells actually combine with the hemoglobin iron to form cuprohemol.

Relation of Hemochromatosis to Chronic Poisoning with Copper.—From what has gone before, it is evident that the experimental lesions produced in rabbits, and to a lesser degree in white rats, rather closely resemble the early lesions of hemochromatosis, at least, there results an early fibrosis of the liver, marked production of hemofuscin followed or accompanied in a few cases by hemosiderin. What are the proofs that copper is responsible for these changes? In our experimental animals, copper administered over long periods by mouth or subcutaneously has been followed by these changes. The control animals fail to show such changes, and animals given alcohol alone failed to show either fibrosis of the liver or the presence of hemofuscin. Relatively large amounts of copper have been found in the livers of these animals with little, or none, in other organs.

On the other hand, it does not necessarily follow that human hemochromatosis is due to chronic poisoning with copper. The experimental evidence is suggestive and the matter should be further investigated. Thus far we have not had the opportunity to analyze fresh liver tissue in a case of hemochromatosis for copper. We are anxiously awaiting such an opportunity. In the light of the experimental evidence, and in consideration of the data presented by Mills [2] of long exposure to copper or brass of patients who later died of the disease, copper poisoning must be considered a probable etiologic factor. We believe that copper poisoning is perhaps one of the causes of pigment cirrhosis in man. Probably some other metals may act in a similar way.

In daily life many opportunities present themselves for the ingestion of small quantities of copper in foods such as in oysters, crabs and other sea animals. This is especially true in certain localities in which water from smelters drains in to estuaries. Oysters grown under these conditions as at Perth Amboy, N. J., have been found to contain as high as 1,487 mg. of copper and 2,903 mg. of zinc per kilogram of oysters (Hiltner and Wichmann).[29] Of course, this is an extreme case and such oysters are not fit for food. No doubt the greatest source for chronic copper poisoning is found in the industries in which men are in daily contact with copper dust and filings. Workers in brass, coppersmiths and telephone linemen are the persons most likely to become poisoned in much the same way as poisoning with lead occurs. Small quantities

29. Hiltner and Wichmann: Zinc in Oysters, J. Biol. Chem. **38**:205, 1919.

of copper found in cow's milk, fresh vegetables and grains are probably of no importance in this regard because of the small copper content.

Relation to Alcohol.—Mallory [25] believed that distilled liquors which often contain small quantities of copper are important in the production of hemochromatosis. Alcohol has long been considered a factor, not only in the production of pigment cirrhosis, but also in ordinary Laennec's cirrhosis. Many authors have emphasized the incidence of an alcoholic history in cases of hemochromatosis, but no one has succeeded in demonstrating any direct relationship between alcohol and the disease. The quantity of copper in distilled liquors is usually small and probably of no more importance than that found in green vegetables and cereals.

Lythgoe, Berry and Hall [30] have determined the copper content of various distilled liquors obtainable in the state of Massachusetts. They found that in 104 samples the copper content varied from 0.05 to 69 mg. per liter. Of the 1,544 samples of liquor analyzed, only 163, or 10.6 per cent, contained copper. The amounts of copper obtained in alcoholic liquors by these authors are comparable to the quantities found in oysters by Rose and Bodansky [24] who obtained from 24 to 60 mg. of copper per kilogram. Lehmann [31] who has done extensive work in the analysis of foods for the presence of copper estimates that the average person ingests about 20 mg. of copper daily, Thresh [32] confirms this, and adds that so long as the total ingested copper does not exceed 100 mg. daily there is no question of injury to health.

Aside from the fact that only about 10 per cent of distilled liquors contain copper, and these in such small amounts that the injurious effect is perhaps negligible, our experimental results indicate that alcohol in some way inhibits the injurious effects of the copper. Both rabbits and white rats given large doses of a mixture of alcohol and copper by gavage over periods ranging from four months to a year stored only one-tenth, or less, as much copper in their livers as animals given copper in their food over a similar period. The amount of hemofuscin was also greatly reduced, in fact, in the livers of white rats scarcely any of this pigment was present after gavaging with alcohol and copper for one year. The increase in fibrous tissue about the periportal spaces in the rabbits treated with alcohol and copper was essentially the same as in those fed copper only. The white rats treated with alcohol and copper showed distinctly less fibrosis than did the rats fed copper only.

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30. Lythgoe, H. C.; Berry, B. O., and Hall, S. H.: The Copper Content of Distilled Liquors on Sale in Massachusetts, Boston M. & S. J. **194**:984, 1926.

31. Lehmann, K. B.: Der Kupfergehalt der menschlichen Nahrungsmittel, Arch. f. Hyg. **24**:1, 1895.

32. Thresh, quoted from Lehmann (footnote 31).

In consideration of the low copper content of distilled liquors and in the light of the experimental data which show that alcohol has an inhibitory effect on the injurious properties of copper, or, what is perhaps more likely, reduces the absorption of copper salts from the gastrointestinal tract, it seems unlikely that consumption of alcoholic beverages containing copper can be responsible for hemochromatosis in man.

CONCLUSIONS

1. Chronic poisoning with copper salts over long periods produces in rabbits a pigment cirrhosis resembling closely the early manifestations of hemochromatosis in man.

2. White rats are less susceptible to chronic copper poisoning than rabbits, the changes produced, though less pronounced, are of the same general character.

3. Rabbits given copper acetate in their food or by subcutaneous injection store relatively large quantities of copper in the liver while only traces of copper can be found in other organs.

4. Each of two sheep that were given copper acetate by subcutaneous injections for twenty-six weeks, stored in his liver 54 per cent of the pure copper administered.

5. Alcohol administered in conjunction with copper acetate not only fails to hasten or augment the production of pigment cirrhosis, but also reduces materially the storage of copper in the liver in both rabbits and white rats.

6. Hemofuscin is produced in the livers of rabbits treated with copper. The quantities of this pigment found closely parallels the copper in any given liver.

7. Hemofuscin contains iron in masked form.

8. Hemosiderin in small amount is seen in a few of the livers of the rabbits. It appears to be derived from hemofuscin. Both pigments are no doubt derived from hemoglobin.

MULTIPLE NECROSIS OF THE SPLEEN

WITH SPECIAL REFERENCE TO THE "SPECKLED SPLEEN" OF FEITIS *

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From a review of the literature, in contrast to the ordinary infarctions of the spleen, multiple necroses have been observed but rarely. Feitis,[1] in 1921, first described two such cases, which he designated under the descriptive term, "Fleckmilz" or speckled spleen. To date, thirteen cases have been reported under this nomenclature (table 1). Clinically, in every case, the condition was not suspected, since direct or indirect symptoms and signs were not apparent. In the study of the clinical histories of the patients, it is interesting to note that the cases fall into two groups: acute (eclampsia and epidemic influenza) and chronic (cardiorenal disease, general arteriosclerosis and hypertension). This corresponds to the two principle forms of the speckled spleen; (*a*) the infectious-toxic-thrombotic (Geipel,[2] Matthias [3] and Wilton [4]) and (*b*) the arteriosclerotic-autotoxic-thrombotic (Feitis, Meuret [5] and Lubarsch [6]). To this may be added a third minor group, the purely toxic form in which thrombosis is absent or is so insignificant that it cannot account for the widespread multiple necroses observed (Enzer [7] and Lubarsch). Matthias agreed with Beneke [8] that as a result of the eclamptic toxin the primary vessel change is an angiospasm with conse-

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* From the Department of the Laboratories, New York Post-Graduate Medical School and Hospital.

* Presented before the New York Pathological Society, at the New York Academy of Medicine, New York, Feb. 9, 1928.

1. Feitis, H.: Ueber multiple Nekrosen in der Milz (Fleckmilz), Beitr. z. path. Anat. **68**:297, 1921.

2. Geipel, P.: Ueber Fleckmilz, Centralbl. f. allg. Pathol. u. path. Anat. **35**:8, 1924-1925; Nierenrindennekrose und Fleckmilz bei Eklampsie, Arch. f. Gynäk. **124**:231, 1925.

3. Matthias: Diskussion zur Vortrag Geipel, Centralbl. f. allg. Pathol. u. path. Anat. **35**:8, 1924-1925.

4. Wilton, A.: Die Fleckmilz (Feitis) und ihre Pathogenese, Frankfurt Ztschr. f. Path. **31**:110, 1925.

5. Meuret, W.: Zur Pathogenese der sogenannte Fleckenmilz, Beitr. z. path. Anat. u. z. allg. Pathol. **73**:525, 1924-1925.

6. Lubarsch, O.: Pathologischen Anatomie der Milz, Berlin, Julius Springer, 1927, vol. 1, p. 447.

7. Enzer, N.: Necrosis of Malpighian Bodies of the Spleen, Am. J. Path., **2**:511, 1926.

8. Beneke, cited by Matthias (footnote 3).

quent endothelial injury and secondary thrombosis. Wilton believed that the necroses do not originate through primary occlusion of the blood vessels but point to a tissue injury of toxic-infectious basis, corresponding to the miliary necroses seen in the majority of infectious diseases, but being quantitatively much more significant. As Enzer's patient did not present arteriosclerotic and thrombotic changes, he ascribed the necroses to a filling of the sinusoids by proliferated, swollen, endothelial

TABLE 1.—*Reported Cases of Speckled Spleen*

No.	Author	Age in Years	Sex	Clinico-Pathologic Diagnosis	Spleen	Type
1	Feitis, 1921	39	M	Chronic interstitial nephritis; uremia; cardiac decompensation; blood pressure, 240	205 Gm.	Feitis
2	Feitis	60	M	Chronic interstitial nephritis; uremia; gout; decompensation; general arteriosclerosis	8 by 4.5 by 1.5 cm.	Feitis
3	Geipel, 1924	35	F	Eclampsia with extensive necrosis of renal cortex	333 Gm.; 12.5 by 9 by 3.5 cm.	Acute
4	Matthias, 1924	..	F	Eclampsia; apoplexy	.....	Acute
5	Wilton, 1925	31	F	Epidemic influenza	650 Gm.	Acute
6	Meuret, 1925	31	M	Secondary contracted kidney; uremia; cardiac decompensation	12 by 7 by 4.5 cm.	Feitis
7	Meuret	46	M	Several apoplectic strokes; general arteriosclerosis; cardiac dilatation and hypertrophy; blood pressure, 200	.....	Feitis
8	Enzer, 1926	59	F	Pernicious anemia; terminal bronchopneumonia	9 by 5 by 3 cm.	Purely toxic
9	Lubarsch, 1927	..	..	Contracted kidneys; general arteriosclerosis; pericarditis; pneumonia	215 Gm.; 14.8 by 6 by 5.3 cm.	Feitis
10	Lubarsch	44	F	Contracted kidneys; general arteriosclerosis; decompensation	105 Gm.; 10.2 by 4.5 by 5.1 cm.	Feitis
11	Lubarsch	52	M	Contracted kidneys; general arteriosclerosis; decompensation; thrombosis of right renal artery and prostatic plexus	130 Gm.; 12 by 6.5 by 3 cm.	Feitis
12	Lubarsch	53	M	Chronic uremia; general arteriosclerosis; emboli into splenic artery; bronchopneumonia	.....	Feitis
13	Lubarsch	51	M	Pernicious anemia	.....	Purely toxic
14	Hosoi, 1928	45	F	Chronic vascular nephritis; general arteriosclerosis; cerebral apoplexy; blood pressure, 230 systolic and 140 diastolic	110 Gm.; 11 by 7 by 4.5 cm.	Feitis

macrophages, which, thus, interfered with the finer circulation of the blood, as was pointed out by Mallory [9] in cases of typhoid fever with focal necrosis in the spleen and liver. Lubarsch considered the arteriosclerotic variety toxic because, in most cases, uremia is present, and he believed the embolic infarct to be autotoxic. According to Feitis, similar spleens are not observed more frequently owing to the marked resistance

9. Mallory, F. B.: Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1920, p. 175.

of the splenic tissues to local ischemia of smaller areas because of their open blood circulation (as shown by Weidenreich,[10] and more recently by Robinson [11] and MacNeal and his co-workers [12]) and their too great abundance of vessels as "blood laboratory."

Although the reported cases are too few to permit any conclusive generalizations, one can see from table 2 that the spleens of the Feitis type tend to be smaller and much lighter than those of the acute type. In the latter type, the recorded ages were 31 and 35, and all were in females; in the former, the ages varied from 39 to 60 and the condition occurred more frequently in males.

The gross and microscopic observations were essentially alike in all cases except Enzer's. Distributed throughout the organ were yellowish to grayish-white, bizarre-shaped areas of firm, cheesy necroses, varying in size from the size of a millet seed to larger than 1 cm. in diameter, with or without infarct-like borders and connected with one another. Microscopic examination showed that the necroses were due

TABLE 2.—*Clinical Data in Reported Cases*

No. of Cases	Speckled Spleen	Age in Years	Sex	Weight in Gm.	Size in Cm.	Clinical Diagnosis
3	Acute type	31 and 35	All females	333 to 650	12 by 9 by 3.5	Eclampsia; influenza
9	Feitis type	39 to 60	6 males, 2 females	105 to 295	8 by 4.5 by 1.5 to 14.8 by 6 by 5.3	Cardiorenal disease; general arteriosclerosis; hypertension
2	Purely toxic type	51 and 59	1 male, 1 female	.....	9 by 5 by 3	Pernicious anemia

to more or less complete occlusion of blood vessels from endarteritis obliterans or thrombosis. There was not any constant relationship between the follicles or the trabeculae and the arrangement of the necrotic areas. Also, the degree of the pathologic processes in the various vessels was apparently without relationship to the position of the necrotic area, because the region nourished by a particular trabecular artery found in the section could naturally lie far removed. In Enzer's case, the necrosis involved a malpighian body in every instance to a more or less varying degree; nowhere was there obliteration of lumen or thrombus formation. The sinuses about the necrotic areas were filled with swollen phagocytic endothelial cells. Wilton considered this

10. Weidenreich, F.: Das Gefässsystem der menschlichen Milz, Arch. f. mikr. Anat. **58**:247, 1901.

11. Robinson, W. L.: The Vascular Mechanism of the Spleen, Am. J. Path. **2**:341, 1926.

12. MacNeal, W. J., and Patterson, M.: The Pathway of Nucleated Erythrocytes Introduced into the Splenic Artery, Proc. Soc. Exper. Biol. & Med. **23**:420, 1926; The Open Circulation of the Spleen Pulp, Am. J. Path. **2**:473, 1926. MacNeal, W. J.; Otani, S., and Patterson, M. B.: The Finer Vascular Channels of the Spleen, ibid. **3**:111, 1927.

necrosis of the malpighian body the precursor of the more advanced process in which there is no significant topographic relationship, the larger necroses being but a fusion of several nodules with extension into the pulp.

In this connection it is interesting to note some of the more or less similar varieties of necroses which are recorded in the literature and which may present a somewhat speckled appearance. Blumer,[13] Blake and Lartigau,[14] Symmers [15] and Karsner [16] called attention to the hyperplasia of the malpighian bodies of the spleen, extensive disintegration of cells of these centers and discharge of nuclear dust into the endothelial sinuses and, finally, replacement by whorllike fibrosis, observed in cases of status lymphaticus. It is to be noted here that Enzer's case somewhat resembles the previously mentioned picture of necrosis of the malpighian body. In the laboratories of the New York Post-Graduate Medical School and Hospital, there was observed a fatal case of bronchopneumonia with necropsy, in a woman, aged 44, in whom the spleen measured 16 by 9 by 7 cm., was deep purple, smooth and soft and showed, on section, numerous, firm, miliary and submiliary, grayish-white specks, of widespread distribution, the largest being 1 mm. in diameter. The pulp was dark red. The microscopic picture was that of focal endothelial hyperplasia in the malpighian bodies with more or less degeneration. Central vessels showed only a hyaline thickening. Nuzum,[17] in 1918, reported four cases of infarction of the entire spleen and found twenty-eight similar cases in the literature. In approximately one half of the total number of cases, the spleen resembled a bag filled with purulent material; in the remainder, the organ was a gigantic scar and was infiltrated with blood pigment. These cases all presented more or less acute symptoms referable to the left hypochondrium. Later in the same year, Richey [18] reported another case of massive infarction in which the spleen, weighing 25 Gm., and measuring 4.8 by 2.2 by 1.8 cm., showed necrosis, with organization and deposition of tiny granules of calcium material and of blood pigment. Multiple caseating tubercles of the spleen can well give it a speckled appearance. In one specimen in our museum, these yellowish areas varied in diameter from that of a millet seed to 5 mm., the confluent ones producing irregular patches.

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13. Blumer, G.: The Relation of the Status Lymphaticus to Sudden Death under Anesthesia and Infection, Bull. Johns Hopkins Hosp. **14**:270, 1903.

14. Blake, J. A., and Lartigau: The Surgical Aspects of the Status Lymphaticus, Ann. Surg. **35**:745, 1902.

15. Symmers, D.: Status Lymphaticus, Am. J. M. Sc. **156**:40, 1918.

16. Karsner: Human Pathology, Philadelphia, J. B. Lippincott Company, 1926, p. 847.

17. Nuzum, F.: The Diagnosis of Infarction of Entire Spleen, J. A. M. A. **70**:283 (Feb. 2) 1918.

18. Richey, D. G.: Massive Infarction of Spleen, J. Lab. & Clin. Med. **3**:519, 1918.

REPORT OF CASE

M. H., a married woman, aged 45, complaining of pain in the right lower quadrant and vomiting of four weeks' duration, following a miscarriage four weeks previously when she was ten weeks pregnant, was admitted to the service of Dr. Charles G. Heyd, who furnished me with an abstract of the clinical history. Her general health had been good; she had not had any operations. She had had eight full-term pregnancies and four miscarriages. Menses began at fourteen, occurred every twenty-three days and lasted five days. Bleeding was moderate. Dysmenorrhea was not present. The last period was fourteen weeks before admission to the hospital. Positive observations on physical examination were: Heart enlarged downward and to the left, a low blowing systolic murmur at the apex and the aortic second sound much accentuated. The blood pressure

Fig. 2.—Low power magnification. Hematoxylin and eosin stain. The intima is markedly thickened in the trabecular arteries. The topmost large artery shows an infiltration of many polymorphonuclear leukocytes. On either side of it are areas of necrosis containing much nuclear dust. The malpighian body at the lower edge contains a completely occluded, hyalinized, central artery. The sinusoids are dilated.

was 230 systolic and 140 diastolic. Expiration was markedly prolonged over the right apex of the lung. There was voluntary rigidity of the abdominal wall. Vaginal examination showed a cystocele, rectocele, lacerated cervix and tender fornices, especially the right. On admission, the blood count was 16,800 white cells, with 79 per cent polymorphonuclears and 21 per cent large and small lymphocytes. The Wassermann reaction was negative. The urine showed four-plus albumin and from 20 to 25 white blood cells per high power field. The icteric index read 10; the van den Bergh reaction was—direct, delayed and indirect, one

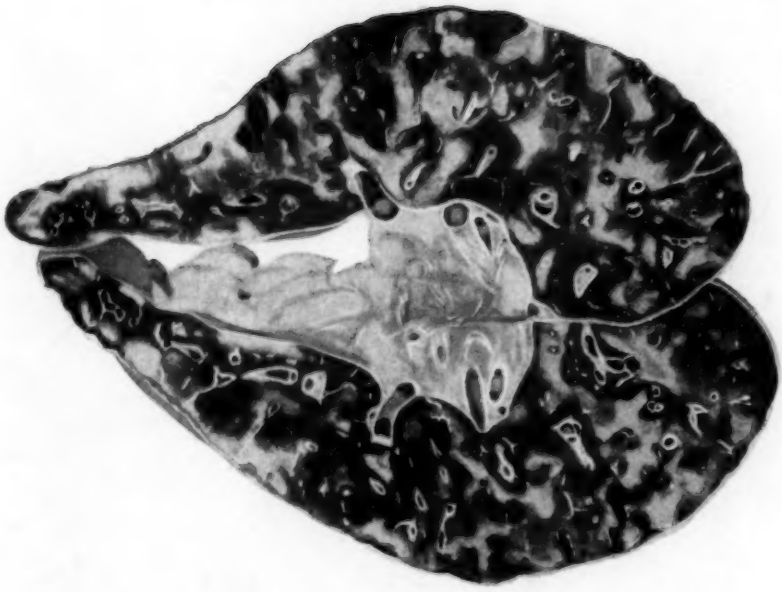

Fig. 1.—Sectioned surface of the speckled spleen, natural size, showing the strikingly characteristic, multiple, bizarre, maplike areas of anemic necroses, with or without a hemorrhagic border. Trabeculae and vessels are prominent. The latter either are empty or contain red or grayish thrombi.

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plus; the Fouchet reaction was faintly positive. The temperature was 99 F., the pulse rate 80, and respiration, 20. A week after admission the patient gradually became drowsy, was difficult to arouse and breathed stertorously. The pupils were widely but evenly dilated. The temperature was 103 F., the pulse rate, 100, and respiration, 20. The white cell count at this time rose to 23,700 with 94 per cent polymorphonuclears and 6 per cent lymphocytes. Death occurred four hours later.

Necropsy.—Necropsy performed one and one fourth hours later showed essentially the following evidence: Large cerebral hemorrhage into the lenticulostriate area, general arteriosclerosis, chronic vascular nephritis, multiple necroses of the spleen, chronic verrucose endocarditis, chronic myocarditis, chronic inactive focal and apical tuberculosis of the lungs, acute ulcerative cholecystitis on a chronic cholecystitis and cholelithiasis, multiple peptic ulcers of the stomach, acute

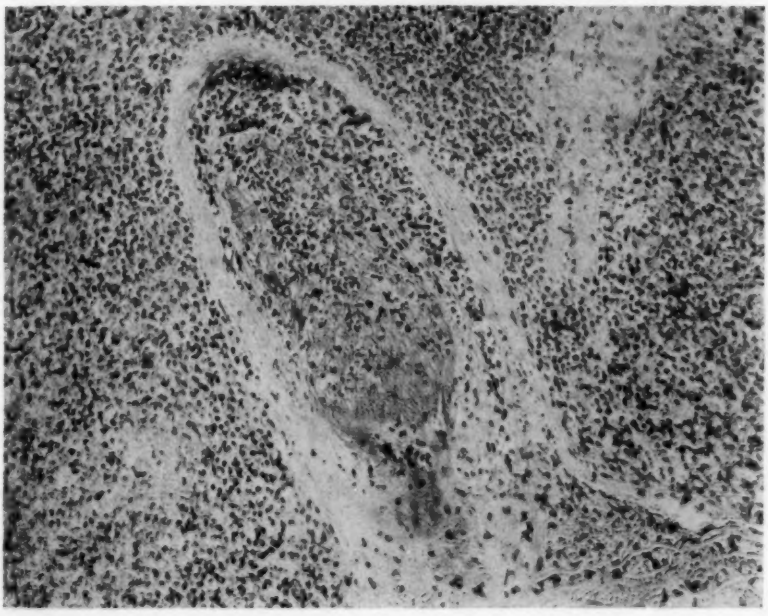

Fig. 3.—Medium power magnification. Hematoxylin and eosin stain. This trabecular artery is completely thrombosed. The wall is infiltrated with numerous polymorphonuclear leukocytes.

pancreatitis with abscess formation on a chronic pancreatitis, chronic obliterative appendicitis, chronic pelvic peritonitis and multilocular cysts of the left ovary.

Gross Description of Spleen.—The spleen weighed 110 Gm., measured 11 by 7 by 4.5 cm. and was firm. Its surface was irregularly and finely nodular. The thin capsule was not adherent to the surrounding structures. The parenchyma beneath showed through as deep bluish-red with still darker red or grayish-yellow mottlings throughout. There was no gritty feeling when the organ was cut into. The sectioned surface was firm, relatively smooth and dark red, containing numerous firm, yellowish islands, irregular as to size and shape and varying in size from that of a pinhead to 3.5 by 10 mm. The yellow areas presented a map-like appearance against the dark red background (fig. 1). Some were infarct-

like with hemorrhagic borders; others merged more or less indistinctly with the surrounding red pulp. The malpighian bodies were invisible. Trabeculae stood out prominently as thin white dots and lines. The vessels, especially the arteries, had thickened walls, were empty or contained red or gray coagulum.

Microscopic Observations.—Under the microscope, it was the necroses which were never isolated, rather than the noninvolved portions that appeared predominant. In the more advanced, more or less structureless central parts of the necrotic areas, fine nuclear dust was scattered about. The malpighian bodies were not discernable, although shadows of hyalinized, occluded vessels could be made out. A thin, often indefinite, hemorrhagic zone separated some of the necrotic from the nonnecrotic regions. In those zones in which degeneration was not so far advanced, the sinusoids were distended with intact red blood cells; here also many polymorphonuclear leukocytes were present among the karyorrhectic nuclei. Frequently, a large patch of hemorrhage appeared to lie between two equally necrotic portions. Owing to the widespread nature of the process, a recognizable relationship between the necroses and the malpighian bodies, blood vessels or trabeculae could not be made out.

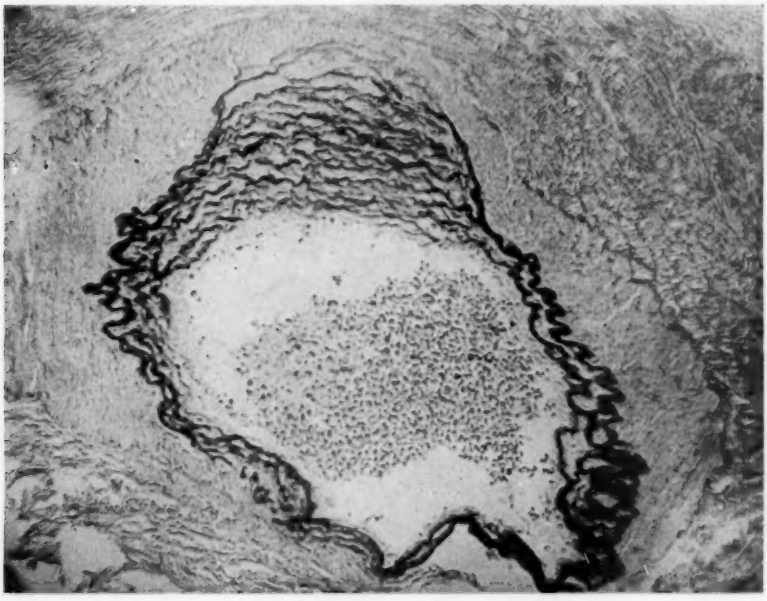

Fig. 4.—Medium power magnification. Weigert's elastic tissue stain. Section shows formation of new elastic lamellae. Where the intima is considerably thickened, the elastic layer is frayed out into many fine fibrillae.

As mentioned before, the nonnecrotic areas appeared as small, widely scattered islands. The sinusoids were dilated, some markedly so. They either were empty or contained more or less intact red blood cells merging insensibly with the hemorrhagic border zone of the necrotic areas. The pulp cords appeared thickened owing to the dilated blood-filled pulp capillaries. Here, fibrosis was not evident, as shown in sections stained by the van Gieson method, in which the light pink areas were limited to the arterioles, capsule and trabeculae. The malpighian

bodies were better preserved but were small, being composed of a narrow zone of lymphocytes around a thickened, hyalinized central artery, obliterated more or less completely (fig. 2). A condensation of lymphocytes was also present about the trabecular arteries.

Blood vessels showed a widespread involvement. The smaller arterioles were completely obliterated by hyalinization or marked intimal proliferation. Others contained an occluding hyaline thrombus. In addition to the foregoing characteristics, which were less marked here in the medium-sized and larger vessels, there was an infiltration of the muscular layer by polymorphonuclear leukocytes (fig. 3), many of which had begun to degenerate, so that numerous nuclear remnants lay strewn about. Often the thickened intimal layers and the hyaline thrombi showed a similar picture of polymorphonuclear infiltration and degeneration, especially in the trabecular arteries. Calcium deposits were not demonstrable in any of the

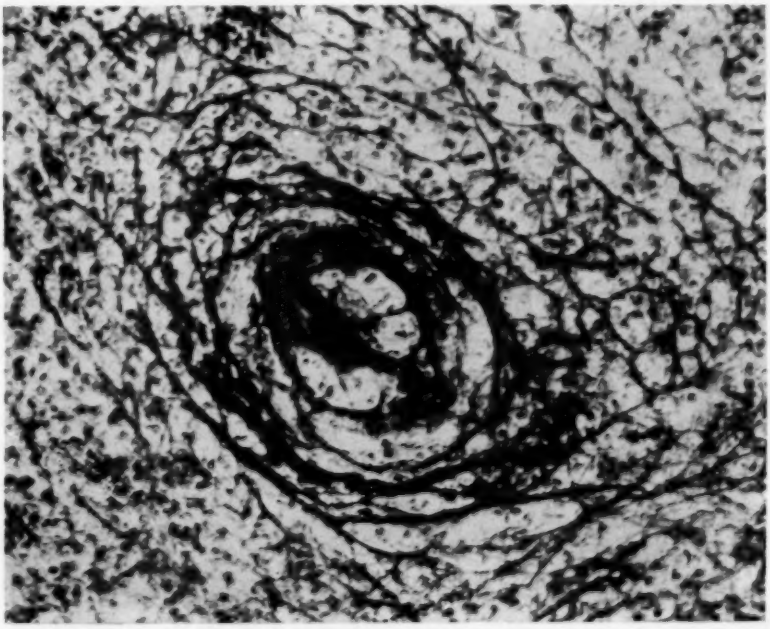

Fig. 5.—High power magnification of a pulp artery. Modified Rio-Hortega silver carbonate stain. The reticular fibers around this vessel are greatly thickened. Reticulum is seen traversing the lumen, completely occluded by organization.

thickened arterial walls. Some lumina occluded by organization were recanalized. The endothelium in some of the almost completely occluded arterioles showed marked hydropic swelling, protruding knoblike into the lumen. By Weigert's elastic tissue stain, the continuity of the internal elastic lamina was shown disrupted beneath the more marked endarterial changes, being replaced by a thickened layer of numerous fine elastic fibrils. Frequently, new internal elastic laminae had been laid down (fig. 4). From the advanced condition of the smaller radicles of the vascular tree and the less involved appearance and occurence of fresh thrombi in the larger branches, it would appear that the process began in the former and gradually extended centripetally.

The capsule and trabeculae were not thickened, not showing increased fibrosis except in those regions in which the walls of the trabecular arteries were infiltrated with polymorphonuclear leukocytes. The elastic elements were well preserved.

For reticulum, the Foot-Menard[19] modification of the Rio-Hortega method was used on paraffin sections and the Magaton[20] modification on frozen fixed sections. These two modifications are practically identical. In the nonnecrotic areas, the fibers occurred in the pulp cords as a fine, lacy network. They were thickened or condensed about blood vessels. In a recanalized arteriole, reticulum was demonstrable in the organization tissue (fig. 5). In the more advanced central necrotic core it was absent, but in the less degenerated areas it occurred as fine to thickened, short, isolated strands, singly or in small branches.

In sections stained with sudan III, lipoid material occurred everywhere as minute droplets, but it was most abundant in the thickened intima of the arterioles and next in the degenerated regions. Much of it was present phagocyted together with or without nuclear remnants, inside of large round, polyhedral or spindle-shaped cells, in which case the droplets tended to be somewhat larger. The minute ones appeared to lie free among the degenerating cells.

Iron pigment, as brought out by Perl's prussian blue method, predominated in the capsule, subcapsular tissues, areas of hemorrhage and thickened intimal layer, as fine granules.

Fibrin in sections stained with Mallory's phosphotungstic-acid hematoxylin occurred most abundantly in the occluding thrombi in blood vessels and hemorrhagic areas, as a closely set, coarse meshwork. In the partially degenerated areas, it was also present here and there as a small fine network with nodal points. It was entirely absent in the central, more necrotic and nonnecrotic areas.

When the Gram method was used, bacteria were not demonstrable after an extensive search through many sections.

SUMMARY

1. Multiple necroses of the spleen, the so-called "Fleckmilz" of Feitis, is rare. To date, only thirteen cases have been reported in the literature.

2. This rarity is due to the marked resistance of the spleen to local ischemia of the smaller areas, because of its open blood circulation and too great abundance of vessels, as "blood laboratory."

3. There are three forms: (*a*) the infectious-toxic-thrombotic, observed in cases of eclampsia and epidemic influenza; (*b*) the arteriosclerotic-autotoxic-thrombotic, in cases of cardiorenal disease, general arteriosclerosis and hypertension, and (*c*) the purely toxic, in cases of pernicious anemia.

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19. Foot, N. C., and Menard, M. C.: Rapid Method for Silver Impregnation of Reticulum, Arch. Path. **4**:211 (Aug.) 1927.

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4. The gross picture is strikingly characteristic. The affected spleen is literally speckled with many firm, yellowish, connecting areas of necrosis, of bizarre shapes and varied sizes with or without infarct-like borders, on a dark red background of variegated intensity.

5. Such a spleen apparently does not produce symptoms or signs recognizable clinically. All cases reported so far have been found accidentally at necropsy.

6. Other conditions like necrosis of the malpighian body in status lymphaticus and multiple caseating tuberculosis of the spleen may show a superficial resemblance to the Fleckmilz of Feitis, but they should not be confused with it.

7. An additional case of speckled spleen of the arteriosclerotic-autotoxic-thrombotic type is reported.

THE FINER STRUCTURE OF THE LUNG

WITH SPECIAL REFERENCE TO ITS VASCULAR CHARACTER AND ITS PATHOLOGIC SIGNIFICANCE *

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A common, time-honored and traditional conception of the lung is that of a gland in which the pulmonary "alveoli" are lined by "respiratory epithelium." Accordingly, the pulmonary capillaries are subordinated, structurally and functionally, to this "glandular" construction, and have, until recently, been neglected somewhat in their anatomic and functional standing and importance. Thus Schafer [1] (1920) compares the lung directly to a "compound alveolar gland," in which trachea and bronchial ramifications correspond to duct systems and the air vesicles to glandular alveoli.

According to Miller [2] (1906 and 1925), two or more air sacs (infundibula) or groups of alveoli open from a common chamber or atrium, and from three to six atria are connected with the ending of an alveolar passage. The latter leads out from the respiratory bronchiole. The terms vestibule and atrium are used interchangeably in the literature. Ogawa's observations [3] (1920), however, led him to the conclusion that the term atrium is superfluous, at least for the human lung. It is generally agreed (Jordan [4] [1920], Schafer [1] [1920] and others) that the alveoli are lined by a "respiratory" epithelium. This epithelium is stated to be of two types; first: flat, nonnucleated, clear protoplasmic plates; and, second: cuboidal, granular epithelial cells. These include "respiratory epithelium," "phagocytic cells," "dust cells," etc. For convenience of description the term "cuboidal" will be used in this paper. A reinvestigation of these structural details tends to shift this current conception of the glandular character of the lung to that of a primarily vascular organ, and it is my purpose in this communication to present briefly the evidence of the older and of more recent investigations into the finer pulmonary structure. It is evident that this is of fundamental importance as regards the mechanism of respiratory function.

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4. Jordan, H. E.: Histology, New York, D. Appleton & Company, 1924, p. 311.

EMBRYOLOGY

Most embryologists agree on the method of development of the parenchyma of the lung. According to Keith [5] (1923), Bailey and Miller [6] (1923) and others, the anlage of the lung appears as a spherical vesicle connected with the digestive tract. The walls of the pulmonary pocket are lined with endoderm which ultimately forms the epithelial lining of the whole respiratory tract from the ciliated epithelium of the trachea to the pavement epithelium lining the alveoli of the lung. By the sixth week, not only the right and left bronchi are formed, but also the chief bronchial ramifications. Each ramification, it is stated, ends as a bud which divides again and again and continues to divide until the fourth month. The terminal buds form the bronchioles and infundibula. The appearance in microscopic section is described as similar to a gland, such as the pancreas or the parotid. At the sixth month, sacular evaginations develop from the infundibula; they form alveoli or air sacs. Keibel and Mall [7] (1912) point out that at about the sixth month the ends of the finer bronchi have a diameter of from only 0.056 to 0.067 mm., and are closely packed; they may already be called alveoli (Kölliker). Merkel [8] (1902) states that the formation of new branches is scarcely to be followed in the later months on account of the abundant foldings of the alveolar walls. The terminal branch of the respiratory tract is lined with endoderm, and it is agreed that this endoderm flattens to form respiratory epithelium.

Ogawa [9] (1920) conducted a comprehensive study of the comparative histology of the alveolar spaces. In addition to other material, he investigated the lungs of embryo rabbits and concluded that these contain primarily only cuboidal cells. As development proceeds, some of these cells become flatter. The final state shows both types of cells, i. e., the cuboidal cells and the nonnucleated plates. He believes that the disappearance of the nuclei of the flat cells is not a sudden loss which occurs with the first inspiration, but rather a gradual event which takes place during the final stages of embryonic life by pyknosis, karyorrhexis, etc. Most nuclei have thus disappeared by the time of birth.

The authors mentioned agree that the alveoli are derived from the terminal part of the bronchial tree and that they are lined by epithelial cells. With few exceptions, therefore, writers subordinate the capillaries

5. Keith, Sir A.: Embryology, New York, Longmanns, Green & Company, 1923.

6. Bailey and Miller: Embryology, New York, William Wood & Company, 1923, p. 360.

7. Keibel and Mall: Human Embryology, Philadelphia, J. B. Lippincott & Company, 1912, vol. 2, p. 482.

8. Merkel, F.: Bardeleben's Handb. der Anat. d. Menschen., 1902.

9. Ogawa: Am. J. Anat. **27**:333, 1920.

to the glandular construction of the lung, and the capillaries are held to course in the so-called "interalveolar septums." Little is to be found, however, beyond traditional repetition as regards the finer structural details of these septums and the exact position and relation of the capillaries to the respiratory surface. But this is clearly of first importance as regards the whole mechanism of gaseous exchange in the lung. The following questions naturally present themselves: What is the position of the so-called alveolar epithelium in relation to these septums; what structural elements enter into the formation of these septums; and, finally, just what is the position of the capillaries in these septums and their relation to the alveolar epithelium? Before proceeding to personal observations on these points, a short review of the phagocytes of the lung may be in order.

PHAGOCYTES OF THE LUNG

Mononuclear phagocytic cells are observed in the pulmonary alveoli with great frequency in various pathologic conditions, and the question naturally presents itself: What relation have these phagocytic cells to the "alveolar epithelium"? The study of these cells has resulted in a vast literature on the subject, of which only an outline need be given here. There are essentially two opinions: the first, the older and traditional, that these cells are desquamated and proliferating epithelium; the second and more recent, that they are septal and mesodermal in origin. Briscoe [10] (1908) concludes that the phagocytic cells are derivatives of the alveolar lining and are probably epithelial in character. Sewell [11] (1918) also accepts these cells as epithelial in origin, although his own observations are not conclusive. Wislocki [12] (1923) injected carbon particles into the circulation and found that they were taken up by clasmatocytes in the lung; he suggests that these clasmatocytes may be derived from one of three sources: (*a*) from the spleen and liver and carried to the lung by the blood stream, or (*b*) from the capillary endothelium or (*c*) from the cells normally present in the stroma of the lung. Müller [13] (1904) and Beitzke [14] (1913) also differ with the opinion that pulmonary phagocytes, as well as the mononuclear cells of the so-called "catarrhal exudate" are epithelial. The former holds that phagocytes are derived from pigmented cells of the interalveolar stroma and regards them as macrophages. Beitzke draws attention to the fact that similar large oval or round cells with eccentric

10. Briscoe, W. J.: J. Path. & Bact. **12**:66, 1908.
11. Sewell, W. T.: J. Path. & Bact. **22**:40, 1918.
12. Wislocki, G. B.: Am. J. Anat. **32**:423, 1923.
13. Müller, F., cited by Kaufmann: Pathologische Anatomie, 1922, vol. 1, p. 285.
14. Beitzke, in Aschoff L.: Pathologische Anatomie, 1921, vol. 2, p. 310.

nuclei and diffusely staining protoplasm, which are abundant in "desquamative" pneumonia, occur also in the exudate of tuberculous meningitis for which an epithelial origin may be excluded. Therefore, while not denying all epithelial origin, he accepts lymphoid or connective tissue derivation for most of them. Foot [15] (1923) and Permar [16] (1924) come to the conclusion that these phagocytes arise from endothelial vascular cells of the capillaries. The most recent study is by Lang [17] (1925), who concludes that these alveolar phagocytes are not epithelial, but mesodermal in origin, and derivatives of the reticuloendothelial system. Here are included the so-called "respiratory cells," "alveolar phagocytes," "macrophages," "dust cells," "heart failure cells," "cuboidal cells," and "septal cells." Lang, therefore, includes the inflammatory phagocytes and those of other pathologic processes under the same septal cell class derivatives. According to him, the endothelial cells of the capillaries do not possess phagocytic qualities, and do not participate in lung reactions—not even in the formation of the tuberculous "epithelioid cells." Lang further concludes that the alveoli are not lined by any respiratory epithelium.

PERSONAL OBSERVATIONS

Technic.—Fixation was performed either with Zenker's fluid or with formaldehyde. The stains employed were hematoxylin-eosin, van Gieson's connective tissue, Wiegert's elastic tissue and silver nitrate. In cases in which the lungs were well enough developed, as in fetus 6, one lung was inflated, thus affording a means of comparing an expanded with a nonexpanded lung.

Human Fetal Lungs.—The gradual process of development in fetal lungs, ranging in age from 1 to 9 months was followed.

Fetus 1: The fetus was 1 cm. in length and about 4 weeks of age At this stage, transverse serial sections showed both lungs as outgrowths from the intestine. The bronchi were seen to be well formed and definitely of epithelial structure. Their epithelial lining was similar to the endodermal lining of the intestine at this stage. A mass of irregularly arranged mesodermal cells surrounded the bronchi. Some of these cells had round nuclei, while others had somewhat elliptical nuclei. The cells having elliptical nuclei were situated particularly around the bronchus (fig. 1).

Fetus 2: The fetus was 4.8 cm. in length and about 5 weeks of age. Sections taken from the lung of this fetus showed a great many bronchial tubes with their epithelial linings. Between the bronchioles mesodermal cells may be seen. The mesodermal cells were definitely of two types, namely, cells with round nuclei and cells with definitely elongated nuclei. The latter appeared to arrange themselves to form capillaries.

Fetus 3: The fetus was 6 cm. in length and about 10 weeks of age. The bronchial system and the mesodermal cells were similar to those in fetus 2, but

15. Foot, N. C.: J. Exper. Med. **37**:139, 1923.

16. Permar, H. H.: J. Med. Research **44**:1, 1924.

17. Lang, F. J.: Arch. f. Exp.: Zellforschung., vol. 11, 1925; J. Infect. Dis. **37**:430, 1925.

appeared more mature. In addition, the sections showed that many blood elements were present in the lumina of the immature capillaries. The cells between the bronchi did not appear to be outgrowths from the bronchial system; such a process could not be recognized in any microscopic field. They were irregularly arranged, and occasionally a capillary seemed to start around the bronchus and to invade the mesodermal cells. The only structure which appeared glandular was the bronchial system with its epithelial cells (fig. 2). The van Gieson stain failed to show any connective tissue. Evidence of the presence of elastic tissue was not discovered with the aid of Wiegert's elastic tissue stain.

Fetus 4: The fetus was 11 cm. in length and 14 weeks of age. The ramifications of the bronchial tree had increased greatly in number. The bronchioles, like those in fetuses 2 and 3, were also surrounded by the same two types of meso-

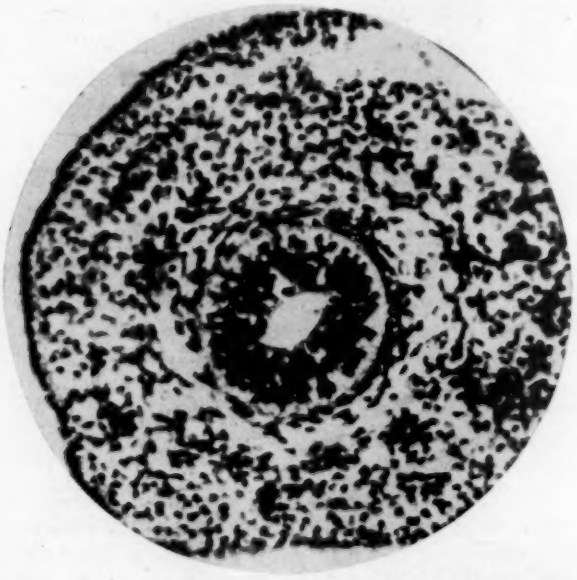

Fig. 1.—Lung of a fetus 1 cm. in length; age about 1 month. Notice the bronchus in the center of the field with mesodermal cells arranged irregularly about it; some of the mesodermal cells are elongated. In this and the following photomicrographs the details are best studied with aid of a magnifying lens.

dermal cells, namely the capillary cells and the round cells. The van Gieson stain showed a slight amount of connective tissue around the larger vessel, but none around the capillaries.

Fetus 5: The fetus was 14 cm. in length and about 15 weeks of age. Staining with hematoxylin-eosin showed numerous "whirls" of cells with elliptical nuclei arranged around an inmmature alveolar lumen. Round mesodermal cells were irregularly arranged among these elliptical cells. Red blood cells could be seen in what appeared to be embryonic capillaries. This was demonstrated better in fetus 6. Van Gieson's stain failed to reveal any connective tissue around capillaries (fig. 3).

Fetus 6: The fetus was 32 cm. in length and about 26 weeks of age. The lungs were removed from the thorax and placed in water; both lungs sank. One

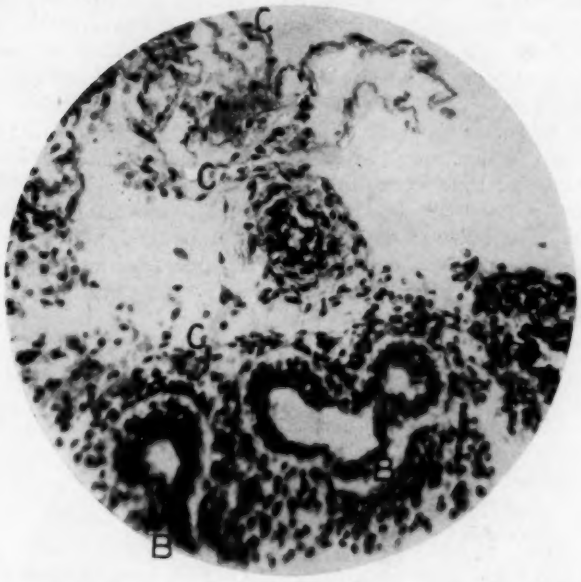

Fig. 2.—Lung of a fetus 6 cm. in length; age about 10 weeks. *B* indicates the bronchus; *C*, the capillaries.

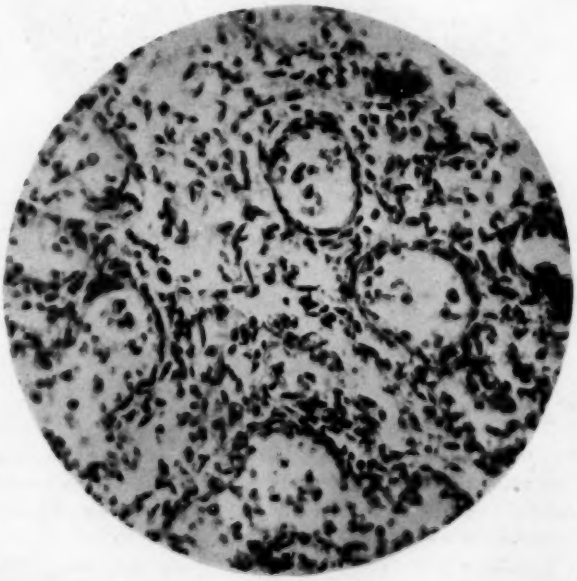

Fig. 3.—Lung of a human fetus about 15 weeks old. Notice "whirls" of what appears to be capillaries with round mesodermal cells irregularly arranged about them.

lung was then inflated with a moderate amount of pressure; this lung floated. Sections were then taken of both lungs. Both sections were studied in order to observe the difference in appearance of an inflated and noninflated lung, because such a difference is to a certain extent analogous to the difference in appearance of a lung during deep inspiration and deep expiration.

Under low power magnification, the microscopic picture of the noninflated lung revealed conspicuous bronchi with deeply stained nuclei. The interbronchial cells were greatly increased in number compared to fetus 5. The small lumina of the air spaces were lined with capillaries filled with blood cells, and scattered here and there a cuboidal cell was seen. The general impression gained was that the capillaries had developed from the mesoderm and that some mesodermal cells with round nuclei had persisted at irregular intervals; such mesodermal cells were cuboidal. The whole section was vascular (fig. 4).

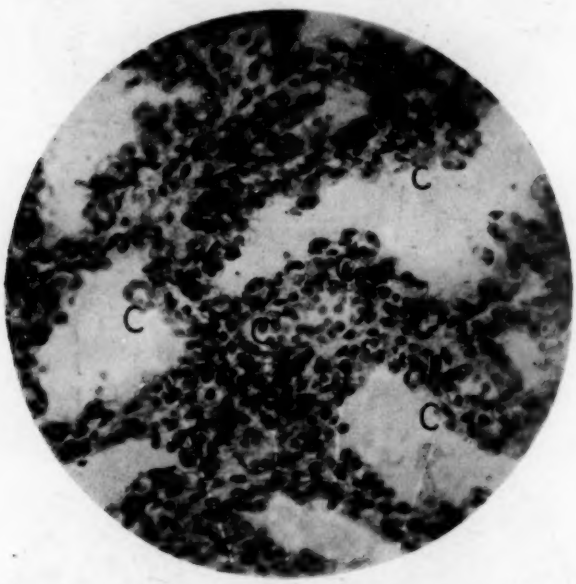

Fig. 4.—Same case as figure 5, but of the other lung which has not been inflated. Notice the capillaries, filled with blood cells, surrounding the air spaces. An occasional "cuboidal" cell may be seen on the capillaries. *C* indicates capillaries containing blood cells.

A section of the inflated lung showed numerous air spaces and many collapsed capillary loops which could be readily recognized by their endothelium with their elliptical nuclei. This agrees with the conclusion of Cloetta[18] (1911 and 1912), who found that the capillaries have a smaller bore in inspiration than in expiration. Van Gieson's stain showed connective tissue around the bronchial system and larger vessels. Connective tissue did not appear to be present around the capillaries or around the air spaces (fig. 5).

FETUS 7: The fetus was 50 cm. in length and was full term. The child was stillborn. The general features of the lungs were similar to those of the lungs in fetus 6, except that the lungs were more vascular and a greater number of

18. Cloetta, M.: Arch. f. exper. Path. u. Pharmakol., 1911, vol. 66; ibid., 1912, vol. 70.

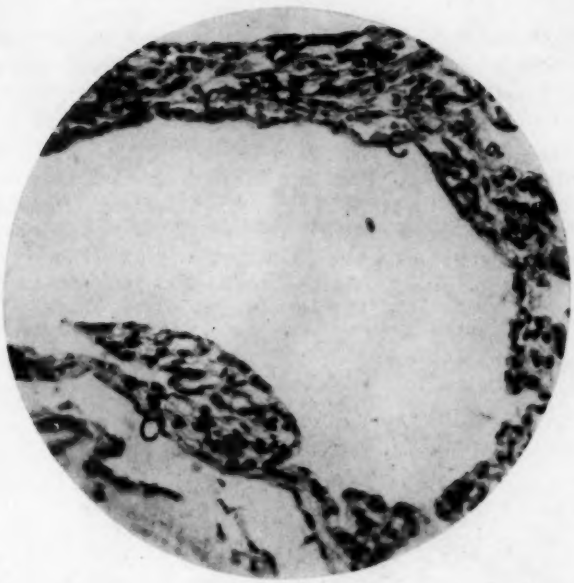

Fig. 5.—Lung of a human fetus about 6½ months old. This lung has been inflated. Notice how the capillaries *"C"* lining the air spaces have collapsed. The capillaries may be recognized by their ellipsoidal nuclei.

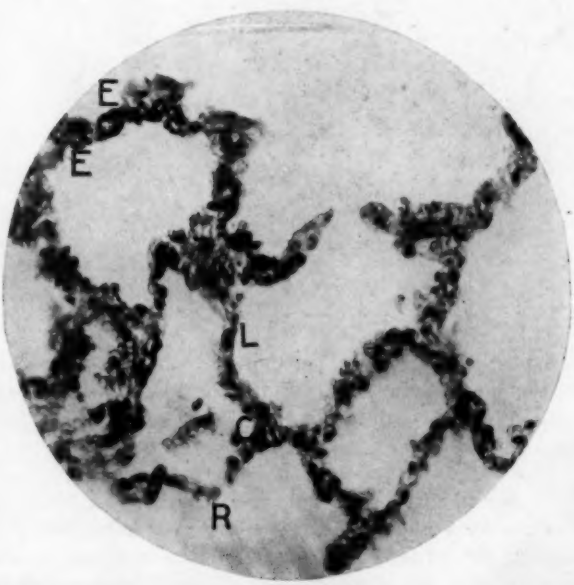

Fig. 6.—Section taken from the crepitant area in a case of lobar pneumonia. The capillaries are congested with blood. Some septums are simply composed of capillary tubes. *R* indicates red blood cells; *C*, cuboidal cells; *E*, capillary endothelium, and *L*, leukocyte in the lumen of a capillary.

capillaries were clearly visible around the air spaces. Weigert's elastic tissue stain showed elastic fibers distributed around capillaries and particularly rich around larger vessels. Van Gieson's stain showed connective tissue around the larger vessels and bronchi but none around the capillaries.

Adult Lungs.—Adult Human Lungs: To study the capillaries in the adult human lungs it is best to obtain specimens in which the capillaries are congested. In one particular case, a snipping of lung was taken from a crepitant area in a case of lobar pneumonia (compensatory emphysema). Microscopic section showed all its capillaries congested with blood, but there was no evidence of pneumonic exudate. In all the lungs examined, the capillaries were prominent and immediately approached the air spaces, with the exception of an occasional intervening

Fig. 7.—Lung of cat killed five minutes after the injection of india ink into the circulation. *C* indicates the capillaries which form the septums with an occasional cuboidal cell. No "alveolar epithelium" is seen on the capillaries. *B* indicates the bronchus opening into the capillary meshwork.

cuboidal cell. No epithelial lining was ever recognized. In places in which capillaries were not filled with blood they were readily identified by their characteristic nuclei (fig. 6). In no instance was it possible to obtain evidence either of lymphatic capillaries or even of definite, continuous perivascular lymph spaces in the interalveolar septums. It would seem, therefore, that the septums do not possess a definite, connected lymphatic system.

Adult Cat's Lung: An instructive picture is reproduced in figure 7. The circulation was injected with india ink. A great many particles lodged in the pulmonary capillaries. They accentuated the vascular system of the lung. It

will be noted that the air spaces are directly lined by loops of capillaries which contain india ink and corpuscular elements. Few septal cells are present in the cat, so that the capillary system appears definite. It may also be noticed that the bronchial system presents the same sharp line of demarcation from the rest of the parenchyma as is characteristic of human lungs.

Adult Dog's Lung: The lung of a dog which had been anesthesized with an impure form of ether was taken for examination. Without repeating details, this lung presented pictures similar to those previously noted in the lungs of human adults and in those of cats.

COMMENT

The embryologic series is not complete, because fetuses ranging in age from about 4 to 6 months were not available. The study of such fetuses might reveal further important data on the histologic structure of the lung. In the specimens studied, however, it may be stated that in no stage in the development of the lung could a characteristic glandular arrangement of alveoli be noticed. The view that the alveoli are formed as a budding growth from the terminal part of the bronchial tree can hardly be entertained on the basis of this histologic material. No evidence of such a process was discovered as the development of the alveoli was traced through various embryonic phases. In the fetuses studied, a cleancut distinction between the bronchial tree and the rest of the lung tissue was maintained throughout. It seems doubtful that this would be the case if the alveoli were really buds from the terminal part of the bronchial tree. Apparently, such a budding does not occur. On the contrary, the bronchi appear to invade the mesodermal mass, and the mesodermal cells around the bronchi then form capillaries; the mesoderm continues to differentiate into capillary loops. Hence the adult lung presents itself as an extensive glomerular capillary network with remaining mesodermal cells at irregular intervals among the capillaries. These cells are in all probability identical with the septal or phagocytic cells already referred to. Here, somewhat as in the kidney, a tubular system (bronchi) is attached to a capillary (glomerular) network. The term "alveolus" suggests a glandular conception of the lung. But, according to our observations, the lung consists of a bronchial system which is distinct from the capillary parenchyma. The capillary appears, therefore, as the essential anatomic and functional pulmonary unit. Heretofore this outstanding rôle of the capillaries has not been sufficiently emphasized on account of the glandular conception of the lung. But it is really the abundant capillary supply which directly furnishes a vast breathing surface. It would, therefore, no longer seem justifiable to subordinate it to a doubtful glandular structure. The term "alveolus," if retained, should be used in the sense of "air space" or "air sinus," rather than in the glandular meaning. This conception of "alveolar" structure also is in greater harmony with "interalveolar communications," as described by Kohn and others.

The exact anatomic significance of the nonnucleated plates has not been definitely established to date. Many authors regard them as a definite cellular entity. On the other hand, Oppel [19] (1905) and Szymonowicz [20] (1909) regard these nonnucleated cells simply as parts of the nucleated cells of the lung. Lange (1909) perfused the lungs of rabbits and collected the desquamated cells. Although this experiment is not conclusive because the source of the cellular elements is uncertain, it is worthy of note that he did not find any nonnucleated plates. In the present investigation no nonnucleated plates were seen when thin microscopic sections were studied. When thick microscopic sections (from 20 to 30 microns) were studied for the demonstration of these cells, as advocated by most authors, the impression gained was that the "cement" lines seen in silver preparations appeared to be due to a great extent to the extensive elastic tissue framework of the lung.

According to the view held hitherto on the development of the lung from endoderm alone, investigators have found it necessary to substantiate the existence of such cells because they were believed to be developed as a flattening out of the terminal part of the bronchial tube. Indeed some observers state definitely that the columnar nucleated epithelial cells are flattened out on the first act of respiration. However, on the basis of these observations which indicate that the lung is developed from two germ layers, endoderm for the bronchi and mesoderm for the capillaries (and cuboidal cells), it is hardly necessary to hypothecate the existence of the flat nonnucleated plates.

If the observations on the inflated and noninflated lungs of fetus 6 are further substantiated, they suggest a direct relation of the capillaries to respiration. While it is not my purpose in this communication to take up functional questions, it may be pointed out that this vascular conception of the structure of the lung gives a somewhat clearer understanding of the immediate importance of the capillary surface in such disorders as dyspnea and cyanotic congestion. Thus when the alveoli are distended, the capillaries are collapsed, and when the alveoli are collapsed the capillaries are distended. Anatomically also this conception of pulmonary structure invites renewed study of the pathogenesis and histogenesis of the lesions in pneumonia, emphysema and tuberculosis.

CONCLUSIONS

Developmentally, the bronchi invade a layer of mesoderm; hence the lung is of dualistic origin.

Mesodermal cells form the capillarly system, and other mesodermal cells persist as septal cells.

19. Oppel: Lehrbuch der vergleichenden mikroskopischen Anatomie, vol. 4, 1905.

20. Szymonowicz: Lehrbuch der Histologie, 1909.

The septal cells are probably not epithelial cells, but persistent mesodermal cells spread irregularly among the capillaries. These mesodermal cells should be classed as part of the reticulo-endothelial system.

Evidence was not found that the alveoli develop as an outgrowth of the bronchial tree.

At no stage in the development of the lung proper could a characteristic glandular arrangement of alveoli be definitely demonstrated.

The capillaries form the essential anatomic and functional unit of the lung (glomerulus).

Evidence of a definite perivascular lymphatic system was not discovered.

NOTE: Since the completion of this paper, publication of which has been delayed, an article by B. M. Fried [21] (1927) has come to my notice. Fried also concludes that the alveolar phagocytes are mesenchymal histocytes, and he expresses doubt concerning the epithelial character of the alveolar lining. In this respect, the embryologic observations here recorded favor this doubt, for they indicate a separate development of pulmonary alveoli from mesenchyme, distinct from the glandular part of the bronchial tree which is endodermal in origin.

21. Fried, B. M.: Arch. Path. & Exper. Med. **3**:751, 1927.

HYPOGASTRO-ETROSCHISIS, SPINA BIFIDA, DIAPHRAGMATIC HERNIA AND LEFT RENAL AGENESIA IN A VIABLE FULL TERM CHILD*

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AND
JAMES D. BALFOUR, M.D.
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In an exhaustive review of the literature, Ballowitz [1] collected 218 instances of agenesia of one kidney. In fifteen cases, doubt is cast on the congenital character of the abnormality because a portion of a ureter was found. Scheuer [2] sheds considerable light on anomalies of the kidney by an excellent discussion of both congenital and acquired defects. The literature abounds in reports of combined renal and genital defects; Holzbach,[3] Schilling [4] and Mohr [5] observed a woman with a diastasis of the pubic bones a handbreadth in width and an exstrophy of the urinary bladder. The present report deals with a combination of defects most closely paralleling those described by Kermauner.[6] The term hypogastro-etroschisis originally suggested by Taruffi in 1894, and cited by Ballantyne,[7] seems the best regional designation for the major anomaly we have to report.

REPORT OF A CASE

History.—As a result of the mother's second gestation, female twins were born at the Cook County Hospital on March 23, 1927. One was apparently normal and at present is living and well. The second twin weighed 2,640 Gm. at birth and had marked malformation. It lived until April 24, 1927, on breast

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* From the Pediatric Service of Dr. Arthur H. Parmalee, Cook County Hospital, and the Norman Bridge Pathological Laboratory of Rush Medical College.

1. Ballowitz, E.: Ueber angeborenen, einseitigen, vollkommenen Nierenmangel, Virchows Arch. f. path. Anat. **141**:309, 1895.

2. Scheuer, L.: Ueber erworbenen und angeborenen nieren Defekte, Ztschr. f. Heilk. **28**:120, 1907.

3. Holzbach, E.: Zur Genese kombinierter nieren-uterus Missbildungen, Monatschr. f. Geburtsh. u. Gynäk. **32**:406, 1910.

4. Schilling, F.: Ueber einseitige defekte im Weiblichen urogenital traktus, Arch. f. Gynäk. **114**:428, 1921.

5. Mohr, L.: Ueber ein fall von Spaltbecken mit ectopia vesicae totales, Monatschr. f. Geburtsh. u. Gynäk. **32**:3, 1910.

6. Kermauner, F.: Ueber Missbildungen mit Störungen des Körpensverschlusses, Arch. f. Gynäk. **78**:221, 1906.

7. Ballantyne, J. W.: Manual of Antenatal Pathology: The Embryo, New York, William Wood & Company, 1905.

and occasional artificial feedings. The following observations were made by Dr. Parmalee while the child was a patient on the pediatric service.

"A small infant with normal head, thorax and extremities, has an enormous skin defect on the anterior abdominal wall. The cord is entirely amniotic. A bluish-gray, parchment-like skin forms the upper portion of the skin defect. The lower portion has a coarsely granular purplish red appearance at the lower margin of which there protrudes a funnel-shaped, wrinkled portion of bowel. At the end of this there is an opening from which normal yellow feces are extruded from time to time. There is no anal opening, not even a dimple where the anus should be. There are no external genitalia. In the region of the inguinal canal on each side, there is a small firm swelling with a pinhead-sized opening at the lower end. From the openings a viscid gray mucus is extruded, exactly like that which normally is expelled from the vagina of new-born females. In the midline on a level with these openings, there is a slitlike dimple, but no opening can be made out with the probe. On the lateral aspect of the skin defect just above the inguinal canals, there is a mulberry-like granulation tissue which bleeds easily and is only moderately firm. No urinary openings can be made out. On the inferior lateral aspects there are deeply pigmented folds of skin which come together just anterior to where the anus should be, like a fourchette. These may be labia. There is no pubic arch present."

Postmortem Examination.—The postmortem examination conducted after fixation in a solution of formaldehyde was as follows: The body was that of a negro female fetus of about seven months' gestation, measuring 18 cm. from the occiput to the coccyx, and weighing 1,580 Gm. The body was markedly emaciated; the neck was twisted to the right and could not be straightened. The fingernails and toenails projected from 1 to 2 mm. beyond the ends of the fingers and toes. The head was covered with short, black curly hair. The skin was dirty brown and wrinkled, with the exception of irregular areas over both deltoid regions, and both forearms and legs on the anterior and posterior aspects. The largest was 3 by 2 cm., the smallest, 5 mm. in diameter. The skin was dirty yellow over these areas, and was not so wrinkled as over the rest of the body. The mouth was open, and the hard and soft palates were normal. The right palpebral fissure was partly open and the left was slitlike. Both nares were patent. There was no superficial lymphadenopathy. The legs were partly flexed and abducted and could not be straightened. The arms were slightly flexed. Interference with the closure of the lower anterior abdominal wall, together with the malformation of the pelvic organs, had resulted in the formation of a cloaca (fig. 1), into which the right ureter and the large bowel opened. The floor of the cloaca was roughened by horizontal parallel ridges, resembling the mucosa of the large bowel. In the lower part of the cloaca was a hernial sac containing part of the small bowel, cecum and appendix (fig. 1 *B*). Situated at the lower lateral aspect of the cloaca (fig. 1 *C* and *D*) were two slightly raised, roughened and deeply fissured cauliflower-like masses. The one on the right side was the external opening of the right ureter. Lower down and more medially (fig. 1 *E* and *G*) were the two small openings of the mullerian ducts. Immediately beneath these were two small, raised, hardened masses, the right measuring 15 by 3 by 2 mm. above the surface, and the left, 17 by 3 by 2 mm. (fig. 1 *F* and *H*). Below these nodules, and extending upward and laterally, were two folds of skin (fig. 1 *I* and *J*).

Both ovaries were in close proximity to the ends of the mullerian ducts near the lateral wall of the pelvis. They were small, roughly oblong, flattened bodies, 1.5 by 2 mm., and were a light yellowish brown. The two mullerian ducts were

2 cm. long along the lateral aspects of the pelvis; they were firm and expanded distally and fused with the posterior aspect of the cloaca. Here the distal ends were 2 cm. apart. Running along the right posterior pelvic wall, lateral to the right mullerian duct was the dilated right ureter, which traced downward along the posterior abdominal and pelvic walls, turned forward and finally fused with the posterior aspect of the cloaca. On the left side, lateral to the left mullerian duct, was a structure which apparently led from the cauliflower mass on that

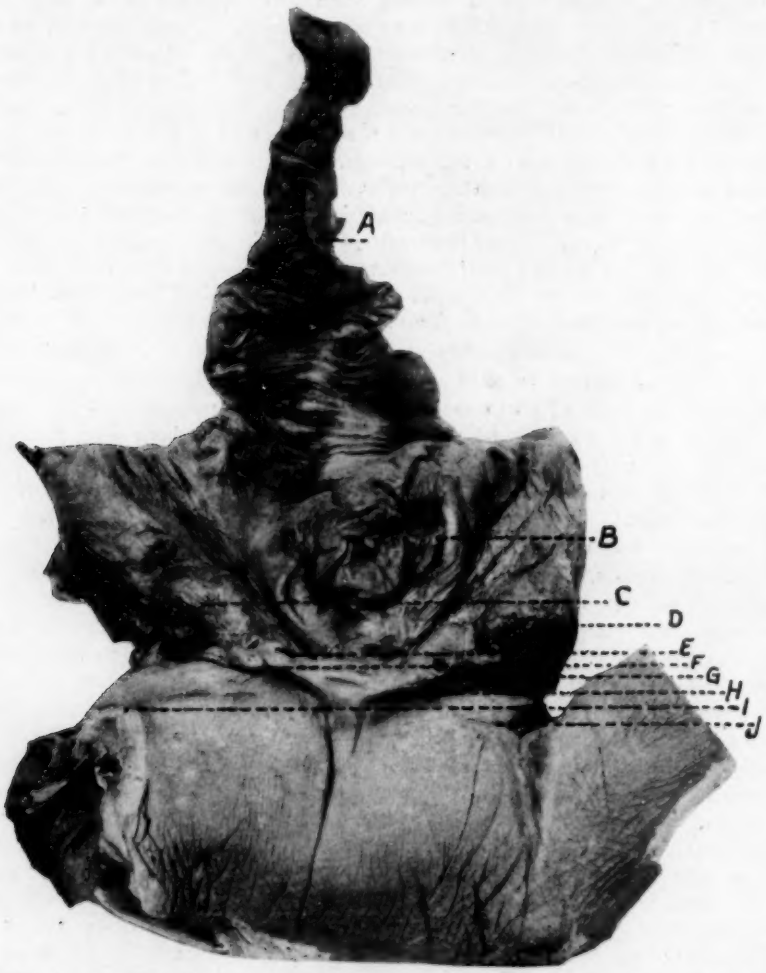

Fig. 1.—Anterior view of the cloaca and defect in the lower anterior abdominal wall. *A* represents the opening of the large bowel into the cloaca; *B*, the hernial sac through the floor of the cloaca; *C*, the external opening of the right ureter; *D*, the cauliflower-like mass on the left; *E*, the external opening of the right mullerian duct; *F*, the elevated hardened area on the right side; *G*, the external opening of the left mullerian duct; *H*, the elevated hardened area on the left side; *I* and *J*, the folds of skin extending laterally.

side. Traced downward, this ended blindly in the posterior pelvic wall. By histologic examination, this was found to be the ureter. In the midline of the pelvis was a hollow structure, with a dilated, rounded, blind end measuring 12 mm. by 14 mm. Traced upward, this structure narrowed, twisted and ended by becoming continuous with the hernial sac in the floor of the cloaca. From the blind end to the orifice measured 20 mm. The diameter at the orifice was 15 mm. The lining of the dilated end was like that of the large intestine; the valvulae conniventes were well marked. Along the narrowed part they were also present but not so well defined. Here they were seen in the long axis. On histologic examination, this structure was found to be the rectum.

The right lung weighed 23 Gm., and was a dull slate gray and semisolid. The surfaces made by cutting were frothy on pressure, being the same color as the external ones. The left lung weighed 22 Gm. and was similar to the right.

Fig. 2.—Posterior view of the pelvis, showing the defect in the posterior surface of the sacrum; and the scoliosis of the vertebral column. *A* represents the defect in the posterior wall of the sacrum.

The heart weighed 13 Gm. and was a dull brownish gray, measuring 3.5 by 2 cm. The musculature of the right outer ventricular wall was 3 mm. thick and that of the left, 4 mm. There was a patent ductus arteriosus. The foramen ovale was closed. On opening the aorta, the posterior wall of the ascending part was found to be markedly invaginated, almost forming a septum. There was no renal artery or vein on the left side. The trachea and esophagus did not present any noteworthy changes.

The liver weighed 70 Gm. and was 7 by 5 by 2.5 cm. It was a dull slate gray, very hard and nodular, deeply fissured and irregular in outline. In the region of the gallbladder, the substance of the liver was stained a bright green, the lobulations being obliterated. The gallbladder was bright green and distended with bile which could not be expressed by pressure. On opening the

gallbladder, the contents were deep green-black and semisolid. The biliary tract was bile-stained, as were also the adjacent gastrohepatic omentum, the pyloric end of the stomach and first part of the duodenum.

The spleen measured 4 by 2.5 cm., weighed 4 Gm., and was dull purple outside. Attached to the upper pole was a small accessory lobe. The parenchyma was deep reddish brown and mottled. The malpighian corpuscles were indistinct. The pancreas was 3 by 7 cm., a dirty yellow-brown, and did not present any noteworthy features. The stomach was empty and dirty gray. The mucosa was normal and near the pylorus was bile-stained. The small intestine was normal, being bile-stained in the region of the ampulla of Vater. The large intestine,

Fig. 3.—View of child during life, showing extent of abdominal defect and herniation of the bowel.

from the opening into the cloaca, was markedly constricted. Thirty-six centimeters from the cloaca there was a well marked volvulus. The mucosa appeared normal.

The right kidney measured 4.5 by 2.5 by 2 cm., weighed 14 Gm. and was a dull slate gray and relatively large and firm with distinct fetal lobulations. On saggital section, the differentiation between the cortex and the medulla was indistinct. The renal pelvis was the same color as the kidney, and leading from it was the dilated ureter previously described. There was no kidney on the left side, nor was there any urinary bladder.

The suprarenal glands together weighed 2 Gm. The left was roughly oblong, measuring 1 cm. by 3 cm. The right one was oval and measured 1.5 by 2.5 cm. in diameter. They were dirty yellow outside and inside had a distinct differentiation between the cortex and the medulla.

The brain weighed 360 Gm. and measured 11 by 8 by 8.5 cm.; it was symmetrical. The lobulations were flattened over the parietal and temporal and occipital areas. In these areas, the substance of the brain was reddish brown and of a jelly-like consistency. The frontal areas were firm and cream-colored. The veins in the leptomeninges were small and not prominent. The arteries at the base of the brain did not present any abnormalities. The cerebellum, medulla and pons were the same color and consistency as the parietal and temporal areas.

There were seven cervical, twelve thoracic and five lumbar vertebrae present. The sacrum was malformed, with an excavation roughly 1.6 cm. in diameter in its posterior surface (fig. 2). There was a marked lumbar scoliosis in the lower left region. The pelvic ring was incomplete, for the pubic bones were 4.5 cm. apart, anteriorly. Laterally, the pubic bones were in the same plane as the vertebral column.

Histology.—Sections stained with hematoxylin and eosin revealed the following: The alveolar walls of the lung were markedly enlarged due to the infiltration of small and large lymphocytes, together with red blood cells. About nine tenths of the alveoli were dilated; the rest were collapsed. The structure on the left side resembling a ureter was composed of muscle tissue, without lumen or epithelium being present. The pouchlike structure in the pelvis was a normal rectum. Section of the spleen and liver stained by the Levaditi method did not show the presence of spirochetes.

The anatomic diagnosis was a composite embodying the original observations on the fresh body by Dr. C. C. Guy, attending pathologist to the Cook County Hospital, and subsequent confirmations and additions by the authors on the preserved specimen.

Anatomic Diagnosis.—Faulty closure of the lower anterior abdominal wall with herniation of the cecum, appendix and small bowel; huge defect in the right leaf of the diaphragm; marked torsion of the liver with partial herniation of the right lobe through the right leaf of the diaphragm; ileofecal fistula with intussusception of the proximal part of the ileum; atresia of both ends of the rectum; absent left kidney and ureter; nonfusion of the mullerian ducts with separate openings in the abdominal defect; volvulus of the large intestine; maldevelopment of the vagina, labia majora and minora, urinary bladder and vulva; marked hypertrophy of the left suprarenal gland; emaciation and prematurity.

EXPERIMENTAL MYOCARDITIC LESIONS IN THE RABBIT

THEIR EFFECT ON MYOCARDIAL ABSCESS FROM INTRAVENOUS INJECTION OF STAPHYLOCOCCI *

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Our purpose is to determine whether the heart of the rabbit in which myocarditis has been produced by the injection of caffeine and epinephrine is more susceptible to bacterial infection than the normal heart of the rabbit.

METHOD

The method employed for the production of the myocarditis was the one used by Fleisher and Loeb,[1] who first described the myocardial lesions caused by single injections of caffeine and epinephrine solutions. We injected 0.2 cc. of 1:1,000 sterilized epinephrine chloride solution (Parke, Davis & Co.) and 0.025 Gm. of caffeine sodium benzoate dissolved in 1 cc. of water. The injections were administered separately in the ear vein, with aseptic technic. They were given slowly during a period of about one minute, for, as previous observers have demonstrated, the number of animals which die of acute edema of the lungs is markedly fewer when the injections are given slowly.

Subsequent to these injections, the rabbits were given intravenous injections of broth culture of *Staphylococcus aureus*, and their organs were examined at varying periods. In all about 100, mainly medium and large sized rabbits, were injected with two laboratory strains of staphylococcus.

Strain A is of rather low virulence. It was found that 5 cc. of a forty-eight hour bouillon culture was sufficient to kill a medium-sized rabbit in two or three days, while 3 cc. caused death in about nine days; 1 cc., however, of the same culture produced abscesses in the kidneys almost constantly but did not kill the animals within three weeks. This strain was used in the majority of our experiments.

Strain A 1 was used in several control series. This strain was received one year after strain A had been obtained. In all probability,

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1. Fleisher, M. S., and Loeb, Leo: Experimental Myocarditis, Arch. Int. Med. **3**:78 (Feb.) 1909.

it is the same as strain A, its virulence having remained essentially unchanged. Thus, 1 cc. of a forty-eight hour bouillon culture produced abscesses in the kidneys in nine out of twelve cases, but did not cause death in any of the rabbits within three weeks.

Strain B was used in only one series of experiments. This strain was considerably more virulent than strains A and A 1. Thus, 1 cc. of a forty-eight hour bouillon culture would kill the majority of the rabbits within one week. Since the results differed considerably in the experiments made with strain A and strain B, the results obtained with these strains will be described separately.

In another paper,[2] we discussed the effects of injections of caffeine and epinephrine hydrochloride on the heart of the rabbit. It may be of interest here, before the combined action of these drugs and of *Staphylococcus aureus* is described, to summarize these observations briefly. In more than 90 per cent of the rabbits injected with epinephrine and caffeine, a rather constant gross lesion appeared in from twelve to twenty-one days. This lesion usually consisted of a pale, firm, yellowish-brown plaque in the myocardium of the anterior aspect of the upper half of the left ventricle, and in some cases it encroached on the left auricle. The right side of the heart and the apex of the left ventricle were never affected. The plaque was raised above the surface of the surrounding myocardium and in many cases did not contract with the rest of the heart muscle. Microscopically, the principal lesions were: (1) interstitial edema, which appeared within a few hours after the injections and increased progressively until it was at its height after from twelve to twenty-one days, after which it decreased in amount; (2) hypertrophy of the muscle fibers and nuclei; (3) degenerative changes in the muscle fibers, which varied in severity from loss of cross striations and increased in intensity of the longitudinal striations to granulation, vacuolization and solution; (4) connective tissue proliferation, especially in the subpericardial and subendocardial areas, between the muscle fibers and around the blood vessels; (5) proliferation of the cells of the endocardium overlying the myocardial lesion; (6) usually sterile fibrinous pericarditis, which later underwent organization; (7) fatty degeneration in the muscle fibers in and around the myocarditic area. The microscopic lesions were usually most marked at from twelve to twenty-one days after the injections.

Abscesses occurred in the heart of rabbits that were given one injection of caffeine and epinephrine solutions and subsequent injections of cultures of *Staphylococcus aureus*.

Twenty-four rabbits were given the usual dose of caffeine and epinephrine solutions, and subsequently were injected intravenously with the

2. Johnson, Scott; and Siebert, Walter J.: Am. Heart J. 3:279 (Feb.) 1928.

forty-eight hour broth culture of staphylococcus of strain A. Of these, sixteen received a single injection of 1 cc. of staphylococcus culture at various periods, ranging from three to fourteen days after the caffeine and epinephrine had been administered. Eight were given four injections each of 1 cc. of the same culture at forty-eight hour intervals, starting at various periods ranging from three to fourteen days after the administration of the caffeine and epinephrine. The rabbits were killed from five to eighteen days after the injections of staphylococcus. At autopsy, twenty-three, or 95.8 per cent, showed a gross myocarditic

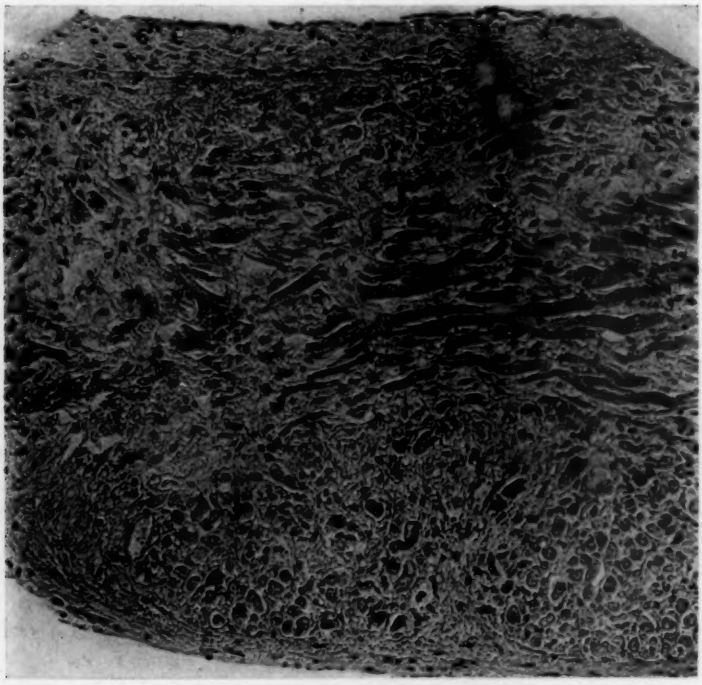

Fig. 1.—Low power section through the left auricle of a rabbit which had been given a single injection of caffeine and epinephrine twenty-one days previously, showing extensive fibrous myocarditis.

lesion produced by the injection of caffeine and epinephrine. Of these, eight showed, in addition, one or more abscesses in the myocardium. The abscesses were situated exclusively in or immediately around the myocarditic area caused by the injection of caffeine and epinephrine in six cases. In two cases, abscesses were found in the normal musculature; however, in both of these cases, abscesses were present at the same time in the myocarditic area.

Sixteen control rabbits receiving injections of only staphylococcus culture were used. Ten were given a single injection each of 1 cc. of

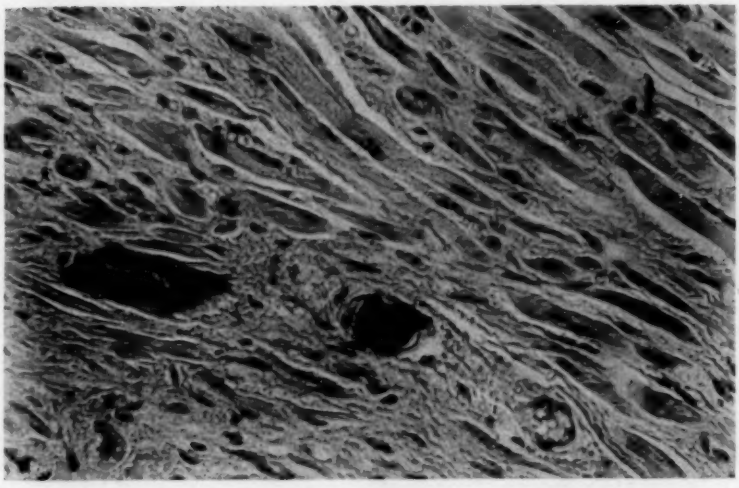

Fig. 2.—High power section showing masses of bacteria lodged in a distorted capillary in the lesion caused by the injection of caffeine and epinephrine in the left ventricle.

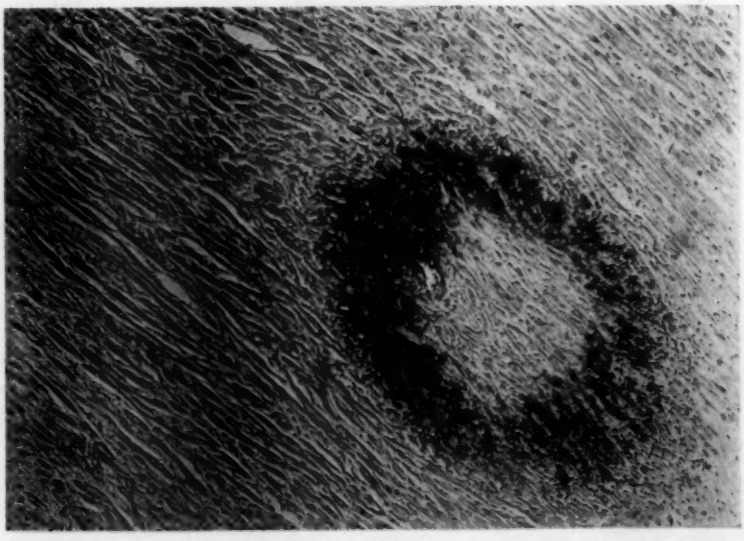

Fig. 3.—Low power section showing the early formation of abscesses in the myocarditic area in the left ventricle caused by the injection of caffeine and epinephrine. Note the masses of bacteria in a distended capillary in the abscess.

a forty-eight hour culture, and six were given multiple injections, as already described. Of these, only one rabbit showed an abscess in the heart, and in this animal there was a preexisting spontaneous myocardial sclerosis near the apex of the left ventricle which predisposed the heart to the formation of an abscess at this site, probably in the same manner in which the lesion caused by the injection of caffeine and epinephrine accomplishes this effect.

In another series of rabbits in which the more virulent strain B was used, ten of eleven animals that had received injections of caffeine and epinephrine showed the lesion produced by these drugs; in addition, and as a result of the injection of staphylococcus cultures, they all developed multiple abscesses in the myocardium which here also had a tendency to be grouped in and around the lesion caused by the injection of caffeine and epinephrine. Of the thirteen control rabbits of this

Data of Distribution of Myocardial Lesions

Injections of Caffeine-Epinephrine and of Staphylococcus, Strain B		Injections of Staphylococcus, Strain B Only	
Number and Position of Abscesses		Number and Position of Abscesses	
Right Ventricle	Left Ventricle	Right Ventricle	Left Ventricle
0	2	12	5
3	8	4	0
8	0	6	6
1	7	4	1
0	2	6	4
Total.. 12	19	32	16

series which received only the staphylococcus culture, ten showed multiple abscesses.

There is therefore no significant difference in the frequency with which the abscesses are found in animals first injected with epinephrine and caffeine and then with the more virulent staphylococcus and in animals injected with staphylococcus alone. However, there is a marked difference in the distribution of the abscesses in these two sets of animals. In order to compare the distribution of the myocardial abscesses in these rabbits, ten hearts, five from each set, all of which showed multiple abscesses, were cut into thin sections with a razor blade, and the abscesses counted and recorded according to their position. The accompanying table presents the results of this examination.

It will be seen from this table that in those cases in which caffeine and epinephrine and staphylococcus were administered, the majority of the abscesses were found in the left ventricle, while in controls which had received only staphylococcus culture, the majority of the abscesses were situated in the right ventricle. There is one exception, however. One rabbit that had received both caffeine-epinephrine and staphylococcus cultures showed eight abscesses in the right ventricle and none

in the left ventricle. A more careful microscopic study of these twelve rabbits revealed another important fact. The abscesses in those rabbits which received only injections of staphylococcus were seldom found in that region of the heart which is usually involved in the lesion caused by the injection of caffeine and epinephrine; when they did occur in the left ventricle, they were usually grouped near the apex, while in the rabbits in which myocarditis caused by the injection of caffeine and epinephrine was present, the abscesses were usually found in or immediately around the lesion caused by the caffeine and epinephrine in the upper half of the left ventricle.

COMMENT

Although we are not able to state definitely the cause of the localization of the abscesses near the myocarditic area, we may suggest several possibilities. It is well known that in areas of newly forming connective tissue small endothelial lined pockets bud off of the capillaries. These are seen especially at the edges of the scarred areas in the myocardium as blind pockets. It is conceivable that bacteria floating free in the blood stream might lodge more readily and in greater numbers in such blind pockets than in normal capillaries, and in this way may account for the localization of abscesses chiefly at the periphery of the chronic myocarditic area, where such distorted capillaries are seen most frequently. Such factors as degenerative changes and necrosis in the heart muscle apparently do not play a rôle of any importance, since the abscesses most frequently localize in areas in which degenerative changes or necrosis are not present. However, after these and various other possibilities are taken into consideration, the first mentioned factor is probably the more tenable, at least until further investigations are carried out.

These experiments justify the following conclusions:

1. The myocarditic lesions produced by injections of caffeine and epinephrine predispose rabbits injected intravenously with cultures of *Staphylococcus aureus* to formation of abscesses in the heart, provided a staphylococcus of low virulence is used.

2. The abscesses thus produced tend to be localized in and around the lesions produced by injections of caffeine and epinephrine.

3. If a more virulent strain of staphylococcus is injected, the myocarditic lesion may not increase the frequency of the formation of abscesses in the heart, but it still determines its localization. Thus, while in previously normal rabbits the abscesses resulting from injections of staphylococcus strain B occur more frequently in the right than in the left ventricle, in animals in which a myocarditic lesion has been experimentally produced in the left ventricle, the abscesses following injections of the same organism are more frequently found in the left ventricle.

Endocarditic Lesions Produced by the Injections of Epinephrine-Caffeine and Staphylococcus Cultures.—A proliferation of the endothelium adjacent to the myocarditic area developing after an injection of spartein and epinephrine in rabbits was first observed by Christian and his co-workers [3] (1911). The lesion is a microscopic one. It consists of the proliferation of the endothelial cells immediately adjacent to the myocarditic area. Christian regarded this as a constant lesion occurring in the majority of the rabbits that he injected with caffeine and spartein. It is probably a common occurrence which apparently can be found whenever the myocarditic lesion encroaches on the overlying endothelium.

Mural thrombi were never observed in the rabbits that had received injections of only caffeine and epinephrine, but they can be produced, as our experiments show, through the subsequent injection of cultures of *Staphylococcus aureus.*

Three of the twenty-three rabbits previously described that had received injections of caffeine and epinephrine and of the less virulent staphylococcus culture showed at autopsy, in addition to the myocarditic area caused by the caffeine and epinephrine, gross endocardial lesions; in two cases these lesions consisted of the formation of a mural thrombus, situated exclusively in the endocardium adjacent to the myocarditic area in the left ventricle. In the third case, in addition to the mural thrombus which was found at the same site, an acute vegetation at the line of closure of the mitral valve was present. The microscopic examination confirmed this observation and, moreover, proved that the vegetation had ulcerated. Masses of cocci were present in the valve leaflet. None of the twelve control animals which received staphylococcus culture of this strain alone showed an endocardial lesion.

In the series in which strain B was used, endocardial lesions occurred much more frequently and were observed not only in the rabbits which had received injections of both caffeine-epinephrine solution and the more virulent staphylococcus culture, but in control animals which were injected with the staphylococcus culture alone. Of the ten rabbits which showed the caffeine-epinephrine myocarditis, and which had been injected with the virulent staphylococcus culture, nine showed endocardial vegetations, while in the thirteen control rabbits which received injections of the same staphylococcus culture only six showed such endocardial vegetations.

As far as the site of the endocardial vegetation is concerned, apparently there is no definite difference in the controls and in the animals injected with both caffeine-epinephrine and staphylococcus. The endo-

3. Walker, I. Chandler, and Christian, H. A.: Experimental Cardiorenal Disease, Arch. Int. Med. **8**:515 (Oct.) 1911.

cardial vegetations were usually multiple whenever they were present, and the mitral valve at the line of closure was the most frequent site of their location, while the wall of the left ventricle was next in frequency; the tricuspid valve and the wall of the right auricle followed in frequency. On the other hand, the aorta and the pulmonary valves were never involved. The most common combination of lesions found was that of the mitral valve and of the wall of the left ventricle, at the base of a papillary muscle. In two of the control rabbits in which strain B was used, the abscesses in the myocardium were more frequent in the right ventricular muscle, while the endocardial vegetations were more frequent in the left ventricle. Moreover, in one of these, the myocardial abscesses were situated exclusively in the right ventricle, while the endocardial vegetations were exclusively on the wall of the left ventricle and on the mitral valve. These observations would indicate that if relatively virulent staphylococci are injected, they are able to produce endocarditic lesions without the aid of the myocardial changes and that the endocarditis in this case, therefore, is not dependent on the myocarditis but is a separate, distinct process. However, from this small series, only tentative conclusions as to this question can be drawn at the present time.

As to the possible cause of this endocardial lesion, the following observations may be of interest: In three rabbits that died of acute edema of the lungs immediately following the injection of caffeine and epinephrine, hemorrhages into the mitral valve were observed. Since these hemorrhages were found in three successive experiments, in which we gave special attention to this change, we suspect that this effect of the injection may be more frequent than our observations so far show. This suggests the possibility that hemorrhages may precede and be responsible for the development of the mitral vegetation. However, we did not observe these hemorrhagic lesions in the mitral valves in animals in which vegetations were present, and it is therefore doubtful whether the hemorrhages in the valves are of importance in the localization of the vegetations.

We conclude, therefore, that:

1. Injections of caffeine and epinephrine into rabbits may cause a proliferation of the endothelium adjacent to the myocardial lesion produced by these drugs.

2. This lesion of the endothelium may lead in some cases to the formation of mural thrombi at this site in case a comparatively nonvirulent strain of *Staphylococcus aureus* culture is injected into the blood stream.

3. When a more virulent strain is used, endocardial vegetations become more frequent, but in this case the vegetations are localized

more frequently on the valves of the heart than on the site of the lesions in the endocardium caused by the injection of caffeine and epinephrine.

4. The acute vegetative endocarditis can therefore develop independently of the caffeine and epinephrine myocarditis.

Pericarditis.—Christian [3] described a fibrous pericarditis which follows the injection of epinephrine and spartein. He termed this process a sterile congestive pericarditis. In rabbits that die of acute edema of the lungs following the injection of caffeine and epinephrine, he found the blood vessels under the pericardium of the left ventricle and left auricle to be deeply congested; occasionally, in this type of case, it was possible to observe grossly a thin exudate of fibrin over the surface of the heart. In the course of time, this fibrin would have become organized by granulation tissue. This lesion that Christian observed after the injection of epinephrine and spartein we have been able to find also in our cases after the injection of caffeine and epinephrine. We have observed subpericardial hemorrhages in several instances following the injection of the latter substances. In only two of thirty-nine rabbits that were injected with caffeine and epinephrine alone and then examined for pericarditis were we able to see grossly a fibrinous pericarditis. However, in twelve of these cases we found an organizing fibrinous pericarditis microscopically. These rabbits were examined at periods varying between three and eighty days following the injections. Cultures of the pericardial sacs were made in six of these cases (among them two which showed a fibrinous pericarditis microscopically), but all the cultures proved to be negative. Rabbits which had bronchopneumonia were excluded from this series, since bronchopneumonia frequently causes a pericarditis, probably by direct extension of the pneumonia process through the pleurae into the pericardium.

Of thirty-five rabbits which had received injections of caffeine-epinephrine solution and staphylococcus culture and which did not show bronchopneumonia at autopsy, a suppurative pericarditis was not found in a single case. Nine additional rabbits that did show pericarditis also showed extensive bronchopneumonia. It is thus difficult to determine in how many of these rabbits the pericarditic lesions were secondary to the bronchopneumonia and in how many it was a direct effect of the injections. We have observed serosanguineous and fibrinous as well as chronic fibrous pericarditis in stock animals which have died of bronchopneumonia; but bronchopneumonia was much more frequent among the rabbits used in our experiments than among the stock rabbits. It was about twice as frequent in rabbits which had received injections of caffeine-epinephrine and staphylococcus as in those which had received injections of staphylococcus alone. It would seem that the

congestion and edema in the lungs produced by the injections directly or secondarily by the caffeine-epinephrine myocarditis may be an important factor in the etiology of the bronchopneumonia.

In order to determine the resistance of the pericardial sac to infection by *Staphylococcus aureus,* five rabbits were injected in the usual way with caffeine and epinephrine, and five days later they each received 1 cc. of a forty-eight hour broth culture of strain A of *Staphylococcus aureus* directly into the pericardial sac. For this purpose the animals were anesthetized with ether, and the pericardial sac was exposed by the resection of several ribs over the base of the heart. The bacterial culture was then injected into the pericardial sac by means of a syringe, aseptic technic being employed. The wound was then carefully closed with silk sutures and was dressed. When examined from four to seven days later, all the rabbits showed grossly the caffeine and epinephrine myocarditis. Three rabbits showed, in addition, an organizing fibrinous pericarditis; only one rabbit had a purulent pericarditis, while a last one did not show any pericarditic lesion.

Of five control rabbits which did not receive caffeine and epinephrine but which received 1 cc. each of a forty-eight hour broth culture of staphylococcus directly into the pericardial sac and which were examined from four to ten days after injection, two rabbits showed an organizing fibrinous pericarditis at autopsy, while two others showed a fibrinous purulent pericarditis. One rabbit did not show a pericarditis. Although the number in this series is small, it does seem that the resistance of the pericardium to bacterial infection is not markedly lowered by previous injection of the rabbits with caffeine and epinephrine solutions. Since two of these rabbits, one that had been given a previous injection with caffeine-epinephrine and one that had not been given such an injection, did not show any pericarditic lesion at autopsy, it would appear that in certain cases the pericardial sac is able to resist an infection by *Staphylococcus aureus.* The lungs did not show lesions in any of these cases.

We may conclude that:

1. An injection of caffeine and epinephrine into rabbits may cause the development of a sterile fibrinous pericarditis, which in the course of time becomes changed into a fibrous pericarditis.

2. Pericarditis thus produced, whether it is fibrinous or fibrous, does not cause an increased tendency to infection in the pericardium when *Staphylococcus aureus* is injected directly into the pericardial sac or intravenously.

3. A frequent complication of bronchopneumonia in rabbits is a serofibrinous pericarditis. The rabbits which were injected with caffeine-epinephrine and staphylococcus had a markedly higher incidence of bronchopneumonia than those which were injected only with staphylo-

coccus culture; again, the latter were markedly more subject to bronchopneumonia than the stock rabbits of the same strain which did not receive injections of either epinephrine-caffeine or staphylococcus.

Edema and Cardiac Decomposition in Rabbits Given Injections.—In view of the marked changes in the heart observed in the rabbits into which we injected various solutions, it was of interest to inquire whether a cardiac decompensation and edema would be caused as a result of these lesions. From this point of view, we examined the twenty-four rabbits previously described which were given injections of caffeine and epinephrine and subsequent injections of *Staphylococcus aureus* culture of strain A. Sixteen of these animals had each received a single intravenous injection of bacterial culture, and eight received four successive injections at forty-eight hour intervals. At autopsy, the lesions that we previously described in the myocardium, endocardium and pericardium were found. Six of these rabbits, five of which had received multiple injections of staphylococcus culture while one had received only a single injection, showed an increased amount of fluid in one or more of the body cavities; but edema of the extremities was not found in any of these cases. If more than 50 cc. of fluid was obtained from the peritoneal cavity, it was considered to indicate ascites. All the rabbits in which an increase in peritoneal, pericardial or pleural fluid was present showed at autopsy a marked caffeine and epinephrine myocarditis in the left ventricle, while two had, in addition, abscesses in the myocardium of the left ventricle as well as endocardial lesions, consisting either of a mural thrombus in the left ventricle or of both a mural thrombus in the left ventricle and a vegetation in the mitral valve. Other signs of cardiac decompensation also were noted among the six rabbits which showed a definite increase in serous fluid in one or more body cavities. Two of them had infarcts in the lungs; in one rabbit we found chronic passive congestion in the liver; two showed congestion of the lungs; two had infarcts of the kidneys, and one showed a septic infarct in the liver.

In none of the eighteen control rabbits that received *Staphylococcus aureus* culture alone was an increase in peritoneal, pericardial or pleural fluid observed. This agrees with the fact that none of these animals had lesions in the heart, although the large majority of them did have abscesses in the kidneys. Since the control rabbits showed abscesses in the kidneys in about the same percentage as those rabbits which had received caffeine and epinephrine and staphylococcus but did not have lesions in the heart, we attributed the increase in serous fluid in the body cavities to the lesions in the heart and not to those in the kidneys, although we cannot exclude the possibility that the latter may have been a contributing factor. Thus one rabbit, in particular, from which 150 cc. of ascitic fluid was obtained and in which congestion of the

lungs and liver was found, did not show any abscesses in the kidney, but it had a marked caffeine and epinephrine myocarditis without any abscesses in the heart. That injections of caffeine and epinephrine alone may cause cardiac decompensation has been pointed out by Fleisher and Loeb. While our observations in this respect agree with theirs, it does appear that the cardiac decompensation is more frequent in rabbits that had received injections of staphylococcus in addition to the caffeine-epinephrine.

Vascular Lesions in the Rabbits Given Injections.—The aorta was examined microscopically in eighteen of the rabbits used in our experiments. Eight of these had received the usual dose of caffeine and epinephrine and subsequent multiple injections of *Staphylococcus aureus* culture, while ten had received a single injection of *Staphylococcus aureus* culture. Only two of these eighteen rabbits showed a lesion in the aorta. One had died immediately following the injection of caffeine and epinephrine. The lesion in this case consisted of a necrosis and calcification in the media. The kidneys were granular, and there was focal scarring near the apex of the myocardium of the left ventricle. The lesion was therefore undoubtedly a spontaneous one. The other rabbit had received multiple injections of *Staphylococcus aureus* culture at forty-eight hour intervals. It was killed twelve days after the first injection. Again the sections of the aorta showed necrosis in the media, and in the myocardium near the apex some focal scarring was noticeable. The aorta appeared normal in the remaining seventeen rabbits in which it was examined microscopically. In no case was a lesion found in the aorta which could be ascribed to the action of caffeine and epinephrine.

CONCLUSIONS

1. The injection of one dose of 0.025 Gm. of caffeine sodium benzoate and of 0.2 cc. of 1 : 1,000 epinephrine chloride solutions caused the appearance of gross myocarditic lesions in more than 90 per cent of the rabbits given such injections and of microscopic lesions in almost all the rabbits. This lesion, when present, constantly localizes in the upper half of the left ventricle, encroaches slightly on the base of the left auricle and involves the base of the papillary muscles of the left ventricle and may cause proliferation of the endothelium of the endocardium adjoining the myocarditic lesion. The latter may render the myocardium at the site of the lesion in the left ventricle noncontractile in certain cases.

2. When rabbits so treated are subsequently injected intravenously with the bouillon culture of a suitable strain of *Staphylococcus aureus*, abscesses in the heart are produced much more frequently than in rabbits not previously injected with caffeine and epinephrine. If a more active

strain of staphylococcus is used, the abscesses occur even in the majority of the control animals. With this strain, also, the experimentally produced myocarditic lesion still influences the localization of the abscesses, which develop in and around the myocarditic area mainly in the left ventricle and in the papillary muscles, and less frequently in the endocardium and in the left auricle.

3. Cardiac decompensation may be produced in rabbits by injection of caffeine and epinephrine alone as a result of the myocarditis thus produced; but the frequency of cardiac decompensation may be increased by subsequent injections of a suitable strain of *Staphylococcus aureus*.

4. The proliferation of the endothelium which occurs adjacent to the myocardial lesion, following the injections of caffeine and epinephrine, appears to predispose the site of this lesion to the formation of mural thrombi in case a comparatively nonvirulent strain of *Staphylococcus aureus* culture is injected into the blood stream subsequent to the injection of caffeine and epinephrine.

5. We were not able to demonstrate any direct relationship between the acute vegetations on the valves of the heart and a lesion of the valves produced by the injections of caffeine and epinephrine.

6. The presence of a myocarditic lesion may indirectly favor the production of a fibrinous pericarditis and of pneumonia. On the other hand, injections of caffeine and epinephrine and the lesions produced thereby apparently do not markedly lower the resistance of the pericardium to the action of bacteria injected into the pericardial sac.

BIOMETRICAL STUDIES IN PATHOLOGY

VI. THE PRIMARY SITE OF CANCERS AND OF OTHER MALIGNANT TUMORS *

RAYMOND PEARL
AND
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BALTIMORE

In the two preceding papers in this series [1] we have presented general discussions of the age, sex and racial distribution of the individuals composing the total necropsied population [1] of the Johns Hopkins Hospital, and of the individuals in that necropsied population who were found at death to have cancer or some other malignant tumor. Before proceeding to the more analytic treatment of the material which is contemplated in our research program, it is necessary to present one further general statistical survey of the cancer data. This will concern itself with the location in the body, or site, of the *primary* malignant growth, which may or may not have metastasized prior to the death of the individual. Throughout the history of the pathologic work at the Johns Hopkins Hospital great pains have been taken to determine, in each case of malignancy, with as great precision as all the evidence permitted, the site of the primary malignant growth. In the present tabulation of the records, the final opinion of the pathologists concerned in the making of the necropsies has been taken as decisive on this point. In other words, the opinion of the biometrician plays no part in the tabulations regarding primary location of tumors. The tables reflect accurately and completely the recorded conclusions of the pathologists. In the present paper these records as to primary location are statistically classified, as in the preceding papers in the series, according to the age, sex and race (white or colored) of the patients.

In the preceding paper in the series, the 816 cases of malignant tumors were classified into two main groups:

I. Carcinomas and epitheliomas.

II. Sarcomas and other forms of malignant tumors not falling into class I.

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* Papers from the Statistical Department of the Johns Hopkins Hospital (no. 9) and from the Institute for Biological Research of the Johns Hopkins University.

1. Pearl, R., and Bacon, A. L.: Biometrical Studies in Pathology: IV. Statistical Characteristics of a Population Composed of Necropsied Persons, Arch. Path. **1**:329 (March) 1926; V. The Racial and Age Incidence of Cancer and of Other Malignant Tumors, ibid. **3**:963 (June) 1927.

In class I (carcinoma) no attempt is made in the present paper to subdivide further as to type of tumor (adenocarcinoma, etc.), for the reason that the basic records do not make such finer classification uniformly possible. At times in the history of Johns Hopkins Hospital great pains have been taken to classify the cancers according to type. At other times emphasis has been placed on other aspects of the matter, and the records contain no statement beyond the simple fact that the growth was a carcinoma. Under these circumstances the soundest procedure seems to be not to attempt to divide the material into finer categories than have uniformly inhered in the records from the start.

The location of the *primary* tumor is specified in tables 1 to 8, according to the following organologic classification:

A. Skin.

B. Alimentary tract and associated glandular organs (liver and pancreas) concerned in digestion and metabolism. The whole alimentary canal from mouth to anus falls in this class. Tumors of the jaws have been put in this class, which is perhaps a dubious procedure, as compared with putting them in class G *infra*. But in every case such tumors are specifically and separately recorded, so that if any one prefers to have them in class G he can easily put them there.

C. Reproductive organs, primary and secondary (I. gonads; II. copulatory organs; III. secondary organs, including breasts, uterus, prostate, etc.).

D. Excretory system (kidneys, bladder, etc.).

E. Respiratory system (lungs, larynx, bronchi, etc.).

F. Endocrine organ (other than sex organs).

G. Skeletal and muscular system.

H. Nervous system and sense organs.

J. Lymphatic system.

K. All other organs of the body not included in the foregoing classes.

This is, in some respects, obviously, an *ad hoc* classification designed to deal specifically with tumor sites, and for no other purpose. At the same time it follows the same general plan as the organologic classification of the causes of death previously discussed by Pearl.[2]

Finally, the material having been arranged in accordance with the foregoing classification, each case is placed in the proper cell in tables 1 to 8, according to age at death, on a decennial grouping.

The totals of tables 1, 2, 5 and 6 do not exactly agree with those given in table 1 of the preceding paper in this series.[1] The reason is that study of the data, since that paper was written, has led to the transfer of two cases in white males, and one case in a white female from the "sarcoma and other" group to the "carcinoma" group.

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2. Pearl, R.: The Biology of Death, Philadelphia, J. B. Lippincott Company, 1922; Studies in Human Biology, Baltimore, Williams & Wilkins Company, 1924.

TABLE 1.—*The Primary Location of Carcinomas in White Males, Classified According to Age at Death*

General Location	Special Location: Region	Special Location: Particular Site	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	80 to 89	No Record as to Age	Total
A. Skin	I. Head and neck	Cheek	..	..	..	..	1	1	..	2	..	..	4
		Ear	..	..	..	..	1	..	..	..	..	..	1
		Face	..	..	..	..	..	1	1	..	..	..	2
		Neck	..	..	..	..	1	1	..	..	..	..	2
		Scalp	..	..	..	..	..	1	..	..	..	1	2
Class A total	All A subclasses		..	..	..	..	3	4	1	2	..	1	11
B. Alimentary tract and associated organs	I. Mouth, including lips, tongue, jaws and pharynx	Mouth	..	..	..	1	..	1	2	..	..	..	4
		Lips	..	..	..	1	1	1	1	..	..	..	4
		Tongue	..	..	..	..	1	6	3	..	..	..	10
		Jaws	..	..	..	..	1	2	..	..	..	..	3
		Pharynx	..	..	..	1	..	1	1	..	..	..	3
		Nasopharynx	..	..	..	..	1	1	..	..	..	..	2
		Tonsil	..	..	..	..	2	..	..	..	..	..	2
		Submaxillary gland	..	..	..	..	..	..	..	1	..	..	1
	Subclass B-I total		..	..	..	3	6	12	7	1	..	..	29
	II. Esophagus	Esophagus	..	..	..	..	6	16	5	1	..	..	28
	Subclass B-II total		..	..	..	..	6	16	5	1	..	..	28
	III. Stomach	Stomach as whole	..	..	..	..	6	3	6	1	..	..	16
		Gastro-esophageal junction	..	..	..	..	..	1	1	..	..	..	2
		Cardiac end	..	..	..	..	1	2	4	..	..	..	7
		Lesser curvature	..	..	1	2	3	3	5	..	..	..	14
		Greater curvature	..	..	..	..	1	5	1	..	..	..	7
		Posterior wall	..	..	..	..	1	..	..	1	..	..	2
		Pylorus and lesser curvature	..	..	..	..	2	..	..	..	..	..	2
		Pylorus and posterior wall	..	..	..	..	1	..	..	..	..	..	1
		Pylorus	..	..	..	4	9	11	9	3	..	..	36
	Subclass B-III total		..	..	1	6	24	25	26	5	..	..	87
	IV. Intestine	"Intestine"	..	..	..	..	1	..	1	..	..	..	2
		Duodenum	..	..	..	..	..	..	1	..	..	..	1
		Papilla of Vater	..	..	..	1	..	..	..	..	..	..	1
		Jejunum	..	..	..	..	1	..	..	..	..	..	1
		Cecum	..	..	..	..	1	1	1	..	..	..	3
		Ileocecal valve	..	..	1	..	..	..	..	..	..	..	1
		Colon	..	..	3	1	1	..	1	..	..	..	6
		Ascending colon	..	..	..	..	1	..	1	..	..	..	2
		Hepatic flexure	..	..	..	..	1	1	1	..	..	..	3
		Transverse colon	..	..	..	1	..	..	..	..	..	..	1
		Splenic flexure	..	..	..	1	..	..	2	..	..	..	3
		Descending colon	..	..	..	..	..	..	..	1	..	..	1
		Sigmoid flexure	..	..	..	..	2	..	1	1	..	..	4
		Rectosigmoid	..	..	..	..	..	2	..	..	..	..	2
		Rectum	..	..	1	1	1	1	3	..	..	..	7
	Subclass B-IV total		..	..	5	5	9	5	12	2	..	..	38
	V. Liver and pancreas	Liver	..	..	1	..	..	2	1	..	..	..	4
		Gallbladder and gall ducts	..	..	..	..	1	2	2	..	..	..	5
		Pancreas	..	..	..	1	3	2	1	1	1	..	9
	Subclass B-V total		..	..	1	1	4	6	4	1	1	..	18
Class B total	All B subclasses		..	..	7	15	49	64	54	10	1	..	200
C. Reproductive organs	I. Gonad	Testis	..	..	1	..	..	..	..	..	..	..	1
	II. Copulatory organs	Penis	..	..	..	..	1	..	..	1	..	..	2
	Subclass C-II total		..	..	..	..	1	..	..	1	..	..	2
	III. Secondary organs	Prostate	..	..	..	..	1	4	10	12	..	..	27
		Breast	..	..	..	..	1	..	1	..	1	..	3
	Subclass C-III total		..	..	..	..	2	4	11	12	1	..	30
Class C total	All C subclasses		..	..	1	..	3	4	11	13	1	..	33

TABLE 1.—*The Primary Location of Carcinomas in White Males, Classified According to Age at Death—Continued*

General Location	Special Location: Region	Special Location: Particular Site	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	80 to 89	No Record as to Age	Total
D. Excretory system	I. Kidney	Kidney	..	..	..	..	..	1	1	..	..	..	2
	Subclass D-I total		..	..	..	..	..	1	1	..	..	..	2
	II. Bladder and urethra	Bladder	..	..	..	3	6	7	9	3	..	..	28
		Urethra	..	..	..	..	..	..	2	..	..	..	2
	Subclass D-II total		..	..	..	3	6	7	11	3	..	..	30
Class D total	All D subclasses		..	..	..	3	6	8	12	3	..	..	32
E. Respiratory system	Respiratory organs	Lungs	..	..	..	1	1	1	2	..	..	..	5
		Bronchus	..	..	..	..	1	1	..	..	..	..	2
		Larynx	..	..	..	2	1	..	1	..	..	..	4
		Antrum	..	..	..	..	..	1	..	..	1	..	2
Class E total	All E subclasses		..	..	..	3	3	3	3	..	1	..	13
F. Endocrine system	Endocrine organs	Suprarenals	..	..	..	1	..	2	..	..	..	..	3
		Hypophysial duct	..	1	..	..	..	..	..	..	..	..	1
Class F total	All F subclasses		..	1	..	1	..	2	..	..	..	..	4
K. All other sites		Peritoneum	..	..	..	1	..	1	..	..	..	..	2
		From teratoma of left flank	..	..	..	..	1	..	..	..	..	..	1
Class K total	All K subclasses		..	..	..	1	1	1	..	..	..	..	3
Grand total, whole table			..	1	8	23	65	86	81	28	3	1	296

TABLE 2.—*The Primary Location of Carcinomas in White Females, Classified According to Age at Death*

General Location	Special Location: Region	Special Location: Particular Site	0 to 0	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	No Record as to Age	Total
B. Alimentary tract and associated organs	II. Esophagus	Esophagus	..	..	..	1	1	..	..	1	..	3
	Subclass B-II total		..	..	..	1	1	..	..	1	..	3
	III. Stomach	Stomach as whole	..	..	..	2	..	1	1	..	..	4
		Cardiac end	..	..	..	..	..	1	1	..	..	2
		Lesser curvature	..	..	..	..	..	1	..	1	..	2
		Pylorus	..	..	..	1	7	5	4	..	..	17
	Subclass B-III total		..	..	..	3	7	8	6	1	..	25
	IV. Intestine	Duodenum	..	..	..	..	1	1	..	..	..	2
		Cecum	..	..	..	1	..	..	1	..	..	2
		Colon	..	..	..	..	..	..	1	..	..	1
		Hepatic flexure	..	..	..	..	..	..	..	1	..	1
		Sigmoid flexure	..	..	1	1	3	1	1	..	..	7
		Transverse colon	..	..	..	..	..	1	..	..	..	1
		Descending colon	..	..	..	..	..	..	1	..	..	1
		Rectum	..	1	..	3	2	1	1	..	..	8
	Subclass B-IV total		..	1	1	5	6	4	5	1	..	23
	V. Liver	Liver	..	..	..	..	..	1	1	..	..	2
		Gallbladder and gall ducts	..	..	..	1	4	9	6	1	..	21
		Pancreas	..	..	..	..	..	2	..	..	..	2
	Subclass B-V total		..	..	..	1	4	12	7	1	..	25
Class B total	All B subclasses		..	1	1	10	18	24	18	4	..	76
C. Reproductive organs	1. Gonads	Ovary	..	1	..	2	7	3	3	1	..	17
	Subclass C-I total		..	1	..	2	7	3	3	1	..	17

TABLE 2.—*The Primary Location of Carcinomas in White Females, Classified According to Age at Death—Continued*

General Location	Special Location: Region	Special Location: Particular Site	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	No Record as to Age	Total
	III. Secondary organs	a. Uterus	..	..	1	9	13	15	7	..	..	45
		b. Breast	..	..	..	4	14	5	5	2	..	30
	Subclass C-III total		..	..	1	13	27	20	12	2	..	75
Class C total	All C subclasses		..	1	1	15	34	23	15	3	..	92
D. Excretory system	I. Kidney	Kidney	..	..	..	..	..	1	1	..	..	2
	Subclass D-I total		..	..	..	..	..	1	1	..	..	2
	II. Bladder and urethra	Bladder	..	..	..	..	..	..	1	..	..	1
	Subclass D-II total		..	..	..	..	..	..	1	..	..	1
Class D total	All D subclasses		..	..	..	..	..	1	2	..	..	3
E. Respiratory system	Respiratory organs	Bronchus	..	..	..	..	..	..	..	..	1	1
		Pleura	..	..	..	1	..	..	..	..	..	1
Class E total	All E subclasses		..	..	..	1	..	..	..	..	1	2
F. Endocrine system	Endocrine organs	Hypophysis	..	..	1	..	..	..	..	..	..	1
		Thyroid	..	..	..	..	..	1	..	..	..	1
Class F total	All F subclasses		..	..	1	..	..	1	..	..	..	2
Grand total, whole table			..	2	3	26	52	49	35	7	1	175

TABLE 3.—*The Primary Location of Carcinomas in Colored Males, Classified According to Age at Death*

General Location	Special Location: Region	Special Location: Particular Site	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	Total
B. Alimentary tract and associated organs	I. Mouth	Tongue	..	..	..	1	1	..	..	..	2
		Tonsil	..	..	..	..	..	..	..	1	1
		Parotid	..	..	..	..	..	1	..	..	1
	Subclass B-I total		..	..	..	1	1	1	..	1	4
	II. Esophagus	Esophagus	..	..	..	..	..	1	..	..	1
	Subclass B-II total		..	..	..	..	..	1	..	..	1
	III. Stomach	Stomach as whole	..	..	..	1	1	2	2	..	6
		Cardiac end	..	..	..	..	..	..	1	..	1
		Lesser curvature	..	..	..	..	2	3	3	..	8
		Greater curvature	..	..	..	..	1	2	..	..	3
		Pylorus	..	..	1	1	4	4	2	..	12
	Subclass B-III total		..	..	1	2	8	11	8	..	30
	IV. Intestine	Papilla of Vater	..	..	..	..	1	..	..	..	1
		Ileum	..	..	..	..	..	1	1	..	2
		Cecum	..	..	1	..	..	..	1	..	2
		Ascending colon	..	..	..	..	..	1	..	..	1
		Hepatic flexure	..	..	..	..	1	..	..	..	1
		Rectum	..	..	1	..	1	1	..	..	3
	Subclass B-IV total		..	..	2	..	3	2	2	..	10

TABLE 3.—*The Primary Location of Carcinomas in Colored Males, Classified According to Age at Death—Continued*

General Location	Special Location: Region	Special Location: Particular Site	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	Total
	V. Liver and pancreas	Liver	..	..	..	..	2	1	..	2	5
		Gallbladder	..	..	..	..	..	1	..	..	1
		Pancreas	..	..	..	1	1	3	1	..	6
	Subclass B-V total		..	..	..	1	3	5	1	2	12
Class B total	All B subclasses		..	..	3	4	15	21	11	3	57
C. Reproductive organs	II. Copulatory organs	Penis	..	..	..	1	..	..	1	..	2
		Scrotum	..	..	..	..	..	1	..	..	1
	Subclass C-II total		..	..	..	1	..	1	1	..	3
	III. Secondary organs	Prostate	..	..	..	..	..	..	2	1	3
		Breast	..	..	..	..	..	1	..	..	1
	Subclass C-III total		..	..	..	..	..	1	2	1	4
Class C total	All C subclasses		..	..	..	1	..	2	3	1	7
D.	II. Bladder and urethra	Bladder	..	..	..	2	1	..	..	1	4
Class D total	All D subclasses		..	..	..	2	1	..	..	1	4
E. Respiratory system	Respiratory organs	Lungs	..	..	..	1	3	..	..	..	4
		Bronchus	..	..	..	..	1	..	..	..	1
		Larynx	..	..	..	..	..	1	..	..	1
		Pleura	..	1	..	..	..	..	..	..	1
Class E total	All E subclasses		..	1	..	1	4	1	..	..	7
Grand total, whole table			..	1	3	8	20	24	14	5	75

TABLE 4.—*The Primary Location of Carcinomas in Colored Females, Classified According to Age at Death*

General Location	Special Location: Region	Special Location: Particular Site	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	Total
A. Skin	II. Limbs	Hand	..	..	..	..	..	..	1	..	1
Class A total	All A subclasses		..	..	.	..	..	..	1	..	1
B. Alimentary tract and associated organs	I. Mouth	Jaws	..	..	..	..	..	1	1	..	2
	Subclass B-I total		..	..	..	..	..	1	1	..	2
	II. Esophagus	Esophagus	..	..	..	..	1	..	..	..	1
	Subclass B-II total		..	..	..	..	1	..	..	..	1
	III. Stomach	Pylorus	..	..	..	1	..	1	1	..	3
	Subclass B-III total		..	..	..	1	..	1	1	..	3
	IV. Intestine	Colon	..	..	1	..	..	..	..	..	1
		Hepatic flexure	..	..	..	..	1	..	..	..	1
		Sigmoid flexure	..	..	..	1	..	1	..	..	2
		Rectosigmoid junction	..	..	..	1	..	..	..	..	1
		Rectum	..	..	..	..	1	..	..	..	1
	Subclass B-IV total		..	..	1	2	2	1	..	..	6

TABLE 4.—*The Primary Location of Carcinomas in Colored Females, Classified According to Age at Death—Continued*

General Location	Special Location: Region	Special Location: Particular Site	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	Total
	V. Liver	Gallbladder and gall ducts	..	..	..	..	..	2	..	..	2
		Pancreas	..	..	..	1	1	..	..	..	2
	Subclass B-V total		..	..	..	1	1	2	..	..	4
Class B total	All B subclasses		..	..	1	4	4	5	2	..	16
C. Reproductive organs	I. Gonads	Ovary	..	..	..	..	4	..	1	..	5
	Subclass C-I total		..	..	..	..	4	..	1	..	5
	III. Secondary organs	a. Uterus	..	..	2	4	9	7	3	..	25
		b. Breast	..	..	1	2	6	3	1	2	15
	Subclass C-III total		..	..	3	6	15	10	4	2	40
Class C total	All C subclasses		..	..	3	6	19	10	5	2	45
D.	II. Bladder and urethra	Bladder	..	..	..	..	1	..	..	..	1
Class D total	All D subclasses		..	..	..	..	1	..	..	..	1
E. Respiratory system		Lung	..	..	..	..	..	1	..	..	1
Class E total	All E subclasses		..	..	..	..	..	1	..	..	1
Grand total, whole table			..	..	4	10	24	16	8	2	64

TABLE 5.—*The Primary Location of Sarcomas and Other Malignant Tumors (Except Carcinomas) in White Males, Classified According to Age at Death*

General Location	Special Location: Region	Special Location: Particular Site	Kind of Tumor	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	No Record as to Age	Total
A.	Skin	Leg	Melanotic sarcoma	..	..	..	..	..	1	..	..	..	1
B. Alimentary tract and associated organs	I. Mouth	Jaw	"Tumor"	..	..	..	1	..	..	..	..	..	1
	II. Esophagus	Esophagus	Sarcoma	..	..	..	..	..	1	..	..	..	1
	IV. Intestine	Intestine	Sarcoma	..	..	1	..	..	..	..	..	..	1
			"Tumor"	..	..	..	1	..	..	..	..	..	1
	V. Liver and pancreas	Liver	Sarcoma	..	..	1	..	..	1	..	..	..	2
		Gallbladder	Sarcoma	..	..	..	..	1	..	..	..	..	1
		Pancreas	Hemangioendothelioma	..	..	..	..	..	..	1	..	..	1
Class B total	All B subclasses			..	..	2	2	1	2	1	..	..	8
C. Reproductive organs	I. Gonads	Testis	Sarcoma	..	..	..	2	..	..	..	..	..	2
			Teratoma	..	..	..	1	..	..	..	..	..	1
	III. Secondary organs	Prostate	"Unidentified tumor"	..	..	..	..	1	..	..	..	..	1
Class C total	All C subclasses			..	..	..	3	1	..	..	..	..	4
D. Excretory system	I. Kidney	Kidney	Sarcoma	1	..	1	..	1	..	..	..	..	3
		Kidney	Tumor (endothelial)	..	..	..	..	1	..	..	..	..	1
		Kidney	Hypernephroma	..	..	..	1	1	3	1	..	1	7
	II. Bladder	Bladder	Mixed cell sarcoma	..	..	1	..	..	..	..	..	..	1
Class D total	All D subclasses			1	..	2	1	3	3	1	..	1	12

TABLE 5.—*The Primary Location of Sarcomas and Other Malignant Tumors (Except Carcinomas) in White Males, Classified According to Age at Death—Continued*

General Location	Special Location: Region	Special Location: Particular Site	Kind of Tumor	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	No Record as to Age	Total
E. Respiratory system	Respiratory organs	Lung	Endothelioma	..	..	..	..	..	..	1	..	..	1
		Pleural cavity	Sarcoma	..	..	1	..	..	..	..	..	..	1
Class E total	All E subclasses			..	..	1	..	..	..	1	..	..	2
F. Endocrine system	Hypophysis	Hypophysis	Tumor with malignant tendency	..	..	..	1	..	..	..	..	..	1
		Hypophysis	Cystic glioma	..	..	1	..	..	..	..	..	..	1
	Suprarenal	Suprarenal	Hypernephroma	1	..	1	1	1	..	1	..	..	5
		Suprarenal	Neurocytoma	1	..	..	..	..	..	..	..	..	1
Class F total	All F subclasses			2	..	2	2	1	..	1	..	..	8
G. Skeletal and muscular system	I. Skeletal	Skull	Mixed tumor	..	..	..	1	..	..	..	..	..	1
			Osteosarcoma	1	..	..	..	..	..	..	..	..	1
		Vertebrae	Sarcoma	..	..	..	1	..	..	1	..	..	2
			Myeloma	..	..	..	..	..	1	1	..	..	2
		Scapular	Sarcoma	..	..	..	..	..	..	..	1	..	1
		Femur	Malignant papillocystomatous tumor	..	..	..	..	..	1	..	..	..	1
		Tibia	Sarcoma	..	1	..	..	..	..	..	..	..	1
		Neck	Sarcoma	..	..	1	..	..	..	..	..	..	1
	II. Muscular and mixed	Buttocks	Sarcoma	1	..	..	..	..	..	..	..	..	1
		Thigh	Sarcoma	..	..	..	..	1	..	..	..	..	1
Class G total	All G subclasses			2	1	1	2	1	2	2	1	..	12
H. Nervous system and sense organs	I. Brain	Brain	Sarcoma	..	1	1	..	1	1	..	..	..	4
			Glioma	6	6	3	9	9	6	..	..	..	39
			"Tumor"	..	..	1	1	..	..	..	..	..	2
	II. Sense organs	Eye	Melanotic sarcoma	..	..	..	1	..	..	..	..	..	1
Class H total	All H subclasses			6	7	5	11	10	7	..	..	..	46
J. Lymphatic system	I. General	Lymph glands	Sarcoma	..	..	2	..	2	1	2	..	..	7
	II. Special	Cervical	Sarcoma	..	..	..	..	..	1	..	..	..	1
		Mediastinal	Sarcoma	..	..	2	1	1	1	..	..	..	5
		Mesenteric	Lymphosarcoma	..	..	..	..	1	..	..	..	..	1
		Retroperitoneal	Sarcoma	..	..	..	1	1	..	1	..	..	3
		Pelvic	Lymphosarcoma	..	..	..	..	..	1	..	..	..	1
		Intestine	Lymphosarcoma	..	1	..	..	..	1	..	..	..	2
		Pancreas	Lymphosarcoma	..	1	..	..	..	1	..	..	..	2
Class J total	All J subclasses			..	2	4	2	5	6	3	..	..	22
K. All other sites		I. Mesentery	Sarcoma	..	..	..	..	..	..	1	..	..	1
		II. Spleen	Sarcoma	..	..	..	1	..	..	..	..	..	1
		"Abdominal cavity"	Teratoma	..	..	..	1	..	..	..	..	..	1
Class K total	All K subclasses			..	..	..	2	..	..	1	..	..	3
Grand total, whole table				11	10	17	25	22	21	10	1	1	118

TABLE 6.—*The Primary Location of Sarcomas and Other Malignant Tumors (Except Carcinomas) in White Females, Classified According to Age at Death*

General Location	Special Location: Region	Special Location: Particular Site	Kind of Tumor	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	No Record as to Age	Total
A. Skin	Skin		Sarcoma	1	..	..	1	..	..	1	..	3
B. Alimentary tract	I. Mouth	Upper jaw bone	Sarcoma	..	..	..	1	..	..	..	..	1
	Subclass B-I total			..	..	..	1	..	..	..	..	1
	IV. Intestine	Ascending colon	Sarcoma	..	..	..	..	..	1	..	..	1
	Subclass B-IV total			..	..	..	..	..	1	..	..	1
Class B total	All B subclasses			..	..	..	1	..	1	..	..	2
C. Reproductive organs	I. Gonads	Ovary	Angiosarcoma	..	..	..	..	1	..	..	..	1
			Sarcoma (melanotic)	..	..	1	..	..	..	..	..	1
			"Neoplasm"	..	1	..	..	..	..	..	..	1
			Teratoma	..	..	..	..	1	..	..	..	1
	II. Secondary organs	Uterus	Sarcoma	..	..	..	..	3	4	..	..	7
		Breast	Sarcoma	..	..	..	1	..	1	..	..	2
Class C total	All C subclasses			..	1	1	1	5	5	..	..	13
D. Excretory system	I. Kidney	Kidney	Sarcoma	..	1	..	..	..	..	..	..	1
		Bladder	Sarcoma	1	..	..	..	..	..	..	..	1
Class D total	All D subclasses			1	1	..	..	..	..	..	..	2
F. Endocrine system	Suprarenal	Suprarenal	"Tumor aberrant adrenal"	..	..	..	..	1	..	..	..	1
			"Neoplasm, adrenal region"	1	..	..	..	..	..	..	..	1
			Adenoma (hypernephroma)	..	..	..	1	..	..	..	..	1
Class F total	All F subclasses			1	..	..	1	1	..	..	..	3
G. Skeletal and muscular systems	I. Skeletal	Sacrum	Sarcoma	..	..	..	1	..	..	..	..	1
Class G total	All G subclasses			..	..	..	1	..	..	..	..	1
H. Nervous system and sense organs	I. Brain	Brain	"Tumor"	..	..	..	2	..	..	..	..	2
			Sarcoma	..	..	..	..	1	..	..	..	1
			Glioma	2	2	5	2	3	1	..	..	15
	II. Sense organs	Eye choroid	Melanosarcoma	..	..	1	..	..	..	..	..	1
		Optic nerve	Glio-fibrosarcoma	..	..	1	..	..	..	..	..	1
	III. Peripheral nerves	Sciatic nerve	Sarcoma	..	..	1	..	..	..	..	..	1
Class H total	All H subclasses			2	2	8	4	4	1	..	..	21
J. Lymphatic system	I. General	Lymph glands	Lymphosarcoma (Hodgkins)	..	..	1	..	..	..	..	..	1
	II. Special	Cervical and mediastinal	Mixed cell sarcoma	1	..	..	..	..	..	..	..	1
		Mediastinum	Leukosarcoma	1	..	..	..	..	..	..	..	1
		Bronchial	Sarcoma	..	1	..	..	..	..	..	..	1
		Mesenteric	Sarcoma	..	..	1	1	..	..	..	..	2
		Retroperitoneal	Cystic sarcoma	1	..	..	..	..	..	..	..	1
			Sarcoma	1	..	..	..	..	..	1	..	2
		Intestine	Lymphosarcoma	..	..	..	..	1	..	..	..	1
		Kidney	Lymphosarcoma	1	..	..	1	..	..	..	..	2
Class J total	All J subclasses			5	1	2	2	1	..	1	..	12
K. All other sites		I. Mesentery and omentum	Sarcoma	..	..	..	..	1	..	..	..	1
		II. "Of uncertain origin" involving skull, ileum, etc.	Sarcoma	..	..	..	..	..	..	..	1	1
Class K total	All K subclasses			..	..	..	..	1	..	..	1	2
Grand total, whole table				10	5	11	11	12	7	2	1	59

TABLE 7.—*The Primary Location of Sarcomas and Other Malignant Tumors (Except Carcinomas) in Colored Males, Classified According to Age at Death*

General Location	Special Location: Region	Special Location: Particular Site	Kind of Tumor	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	Total
C. Reproductive organs	I. Gonads	Testis	Adenosarcoma	..	..	..	..	1	..	1
Class C total	All C subclasses			..	..	..	..	1	..	1
D. Excretory system	I. Kidney	Kidney	Hypernephroma	..	..	..	..	..	1	1
Class D total	All D subclasses			..	..	..	..	..	1	1
F. Endocrine system	Suprarenal	Suprarenal	Sarcoma	..	1	..	..	..	..	1
Class F total	All F subclasses			..	1	..	..	..	..	1
G. Skeletal and muscular system	I. Skeletal	Sphenoid	Sarcoma	..	1	..	..	..	..	1
		Vertebral column	Sarcoma	..	..	1	..	..	..	1
		"Heel"	Sarcoma	..	..	..	..	1	..	1
Class G total	All G subclasses			..	1	1	..	1	..	3
H. Nervous system and sense organs	I. Brain	Brain	Glioma	..	..	1	..	..	..	1
		Spinal cord	Diffuse sarcomatosis	1	..	..	..	..	..	1
Class H total	All H subclasses			1	..	1	..	..	..	2
J. Lymphatic system	I. General	Lymph glands and spleen	Mixed cell sarcoma	1	..	..	..	..	..	1
		Lymph glands	Sarcoma	..	..	1	1	..	..	2
	II. Special	Cervical, axillary and mediastinal	Lymphosarcoma	..	..	..	..	1	..	1
		Mesenteric and retroperitoneal	Lymphosarcoma	..	..	..	..	..	1	1
		Retroperitoneal	Sarcoma	..	..	..	..	..	1	1
Class J total	All J subclasses			1	..	1	1	1	2	6
Grand total, whole table				2	2	3	1	3	3	14

TABLE 8.—*The Primary Location of Sarcomas and Other Malignant Tumors (Except Carcinomas) in Colored Females, Classified According to Age at Death*

General Location	Special Location: Region	Special Location: Particular Site	Kind of Tumor	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	Total
A. Skin	I. Skin	Nose	Fibrosarcoma	1	..	..	..	..	..	..	1
	III. Trunk	"Above buttocks"	Sarcoma	..	..	..	..	..	1	..	1
Class A total	All A subclasses			1	..	..	..	..	1	..	2
B. Alimentary tract	I. Mouth	Upper gum	Mixed tumor (parotid type)	..	..	..	..	1	..	..	1
		Pharynx	Sarcoma	1	..	..	..	..	..	..	1
Class B total	All B subclasses			1	..	..	..	1	..	..	2
C. Reproductive organs	I. Gonads	Ovary	Sarcoma	..	1	..	..	..	..	..	1
	III. Secondary organs	a. Uterus	Myosarcoma	..	..	..	..	1	..	..	1
			Sarcoma	..	..	1	..	1	..	..	2
		b. Breast	Sarcoma	..	..	..	..	..	1	..	1
Class C total	All C subclasses			..	1	1	..	2	1	..	5
D. Excretory system	I. Kidney	Kidney	Sarcoma	1	..	..	..	..	..	..	1
	II. Bladder	Bladder	Sarcoma	..	..	..	..	1	..	..	1
Class D total	All D subclasses			1	..	..	..	1	..	..	2
H. Nervous system	I. Brain	Brain	Glioma	1	..	..	..	..	..	..	1
Class H total	All H subclasses			1	..	..	..	..	..	..	1
J. Lymphatic system	II. Special	Peripancreatic lymph glands	Sarcoma	..	..	..	1	..	..	..	1
		Mediastinal and pericardial	Lymphosarcoma	..	..	..	..	..	..	1	1
Class J total	All J subclasses			..	..	..	1	..	..	1	2
K.	All other sites	Bone marrow	Multiple myeloma	..	..	..	..	..	1	..	1
Class K total	All K subclasses			..	..	..	..	..	1	..	1
Grand total, whole table				4	1	1	1	4	3	1	15

THE RELATIVE FREQUENCY OF PRIMARY OCCURRENCE OF MALIGNANCY AT DIFFERENT SITES

Table 9 has been prepared from the raw data of tables 1 to 8, inclusive. This table gives, for each of the four sex and race groups, the percentage frequency of (*a*) carcinomas, (*b*) sarcomas and (*c*) all malignant tumors, in each of the ten broad organ locations *A* to *K*, inclusive.

From table 9 it is plain that the malignant tumors in this necropsied population have their primary location in the alimentary tract and its associated glandular organs (pancreas, gallbladder, gall ducts and liver) more frequently than at any other site, *in male persons,* both white and colored. On the other hand, *in females,* the organ system in which malignant growths most frequently occur is the reproductive system (including both primary and secondary sex organs together), with the alimentary tract in the second place. If, in some manner or other, malignancy of the alimentary tract and of the reproductive organs could be prevented, cancer would retire at once to a relatively unimportant place among the causes of death.

While it is not possible to make an exact comparison of a general population with this necropsied population in respect of the distribution of the data shown in table 9, because official vital statistics are not tabulated in a way to permit it, nevertheless, in a broad way, the data from the United States Registration Area regarding cancer in 1914 [3] agree with the conclusions stated in the preceding paragraph.

The greatest discrepancy between the general population and the necropsy statistics is in respect of cancer of the skin. Patients with cancer of the skin die at home rather than in a hospital relatively more frequently than do patients with cancer of any other organ system. This fact means that such cases tend to be under-represented in necropsy statistics. Table 10, which we have computed from data given in appendix B (p. 509) of the Registrar-General's Statistical Review of England and Wales (tables, part I, Medical), gives the percentage of persons dying in hospitals from cancer at different sites, out of all persons dying from cancer at the same sites.

Table 10 shows in a striking way how much more marked is the tendency to die outside hospitals among persons with cancer of the skin than among persons with cancer of any other organ. The reason for this is plain. The patient who enters a hospital with cancer of the skin in an early stage is discharged cured. But for the patient who lets his cancer of the skin go without treatment, or with only the

3. Mortality from Cancer and other Malignant Tumors in the Registration Area of the United States in 1914, Washington (Bureau of the Census), 1916.

TABLE 9.—*Percentage Frequency of Each Class of Malignant Tumor by Site, Sex and Race. Necropsied Population*

Location of Primary Tumor	White Males			Colored Males			White Females			Colored Females		
	I Carcinoma	II Sarcoma and Other Tumors	III All Malignancy	I Carcinoma	II Sarcoma and Other Tumors	III All Malignancy	I Carcinoma	II Sarcoma and Other Tumors	III All Malignancy	I Carcinoma	II Sarcoma and Other Tumors	III All Malignancy
A. Skin	3.72	0.85	2.90	.....	.....	.....	.....	5.08	1.28	1.56	13.33	3.80
B. Alimentary tract, liver and pancreas	67.57	6.78	50.24	76.00	.....	64.04	43.43	3.39	33.33	25.00	13.33	22.78
C. Reproductive organs, primary and secondary	11.15	3.59	8.94	9.33	7.14	8.99	52.57	22.03	44.87	70.31	33.33	63.29
D. Excretory system	10.81	10.17	10.63	5.35	7.14	5.62	1.71	3.39	2.14	1.56	13.33	3.80
E. Respiratory system	4.39	1.69	3.62	9.33	.....	7.87	1.14	.....	0.85	1.56	.....	1.27
F. Endocrine organs other than sex	1.35	6.78	2.90	.....	7.14	1.12	1.14	5.08	2.14	.....	.....	.....
G. Skeletal and muscular system	.....	10.17	2.90	.....	21.43	3.37	.....	1.69	0.43	.....	.....	.....
H. Nervous system and sense organs	.....	38.98	11.11	.....	14.29	2.25	.....	35.59	8.97	.....	6.67	1.27
J. Lymphatic system	.....	18.64	5.31	.....	42.86	6.74	.....	20.34	5.13	.....	13.33	2.53
K. All other organs	1.01	2.54	1.45	.....	.....	.....	.....	3.39	0.85	.....	6.67	1.27
Totals	100.00	99.99	100.00	99.99	100.00	100.00	99.99	99.98	99.99	99.99	99.99	100.01

TABLE 10.—*Proportion of Deaths from Cancer Occurring (in the Civilian Population) in Hospitals in England and Wales, 1921-1925*

Cause of Death	Males					Females				
	London, per Cent	County Boroughs, per Cent	Other Urban Districts, per Cent	Rural Districts, per Cent	England and Wales, per Cent	London, per Cent	County Boroughs, per Cent	Other Urban Districts, per Cent	Rural Districts, per Cent	England and Wales, per Cent
Cancer (all forms)	22.8	15.6	15.3	12.2	15.8	18.9	10.9	11.4	9.2	11.8
Buccal cavity	19.8	9.6	10.5	7.6	11.0	21.3	9.5	10.3	7.7	10.7
Pharynx, esophagus, stomach, liver and adnexa	20.8	14.2	12.7	9.5	13.6	16.2	9.0	8.7	6.7	9.2
Peritoneum, intestines and rectum	23.6	19.7	19.7	16.1	19.4	20.7	15.7	16.0	12.7	15.8
Female genital organs.	....	....	....	....	....	19.9	10.9	11.9	12.1	12.7
Breast	20.0	12.2	6.5	11.1	11.3	15.9	7.4	8.1	5.6	8.4
Skin	15.6	7.4	7.7	6.0	7.8	15.0	5.2	5.8	2.7	5.7
Other or unspecified organs	26.7	18.5	18.4	15.6	19.4	24.7	14.6	15.8	12.8	16.0

supposedly palliative treatment of quackery, until it is destined shortly to be fatal, a hospital has little to offer.

Table 9 brings out clearly the difference between carcinoma and sarcoma in respect of primary location. No such tendency to concentrate on particular organ systems can be observed in the noncarcinomatous malignant tumors as has been shown to obtain with carcinomas relative to the alimentary tract in males, and to the reproductive system in females. The apparent concentration of the noncarcinomatous tumors on the brain is, as has already been emphasized in an earlier paper in this series, statistically spurious, arising mainly from the great interest in brain surgery in the Johns Hopkins Hospital in recent years.

It is a fact of some interest that in these 816 cases of malignant tumors, there was but one case of multiple primary malignant growths (epithelioma of the esophagus, with hypernephromas of the left kidney in a white male). There were two other cases in which there was a suggestion that such multiple primary tumors had occurred. But a more careful study led to the conclusion that these were really cases of metastasis of a single primary tumor. This conclusion is of interest in connection with the recent paper by Murray,[4] in which he emphasizes the rarity of such occurrences. The case is different, of course, if both malignant and benign neoplasms are taken into the reckoning. A majority of all persons attaining the age after which cancer is of frequent occurrence bear benign tumors of some sort, somewhere in their bodies.

One of the most thorough analyses which has been made regarding the location of carcinomas as revealed in necropsy statistics, is that for the Binnen-Gasthuis in Amsterdam, by De Vries.[5] His table XIV (p. 233) gives the location of 1,215 cases of "cancer" (from internal evidence of this paper this means carcinoma only). Whether the sites tabulated are solely those of primary growths is nowhere clearly stated, but we have assumed that this is what the table means. For the sake of comparison we put the data of De Vries' table XIV against the Johns Hopkins Hospital experience, for white persons in the necropsied population having carcinoma, deriving the data from tables 1 and 2 of this paper. The results are exhibited in table 11.

Table 11 emphasizes the point made by De Vries that selective factors operating in the determination of the kind of patients admitted to a hospital will be reflected in the necropsy statistics of that hospital. The Binnen-Gasthuis does not contain the university clinic of obstetrics and gynecology. This fact, presumably, in some degree accounts for

4. Murray, J. A.: Lancet **213**:800, 1927.
5. De Vries, W. M.: Surg. Gynec. Obst. **44**:217, 1927.

the smaller proportion of cancers of the uterus and female breast in the experience of that hospital than in the Johns Hopkins experience. Also, in the Johns Hopkins Hospital, there has undoubtedly been a selection in favor of cancers of the breast in white females. Similarly, the higher proportion of cancers of the prostate and bladder in the Johns Hopkins experience may be the effect of selection. Altogether, the data of table 11 emphasize once more the fact that no definite conclusion can be drawn from the necropsy experience of any single

TABLE 11.—*Comparing the Necropsy Experiences of the Johns Hopkins Hospital in Respect of the Site of Primary Carcinomas in Whites with that of the Binnen-Gasthuis in Amsterdam (De Vries, 1927)*

Site	White Males Johns Hopkins		White Males Amsterdam		White Females Johns Hopkins		White Females Amsterdam	
	Absolute Number	Per Cent	Absolute Number	Per Cent	Absolute Number	Per Cent	Absolute Number	Per Cent
Stomach	87	29.4	306	38.1	25	14.3	127	30.5
Esophagus	28	9.5	136	17.0	3	1.7	16	3.8
Intestine	38	12.8	103	12.9	23	13.1	68	16.3
Tongue	10	3.4	23	2.9	..	....	...	....
Larynx	4	1.4	27	3.4	..	....	1	0.2
Uterus	..	....	...	....	45	25.7	27	6.5
Breast	3	1.0	1	0.1	30	17.1	48	11.5
Skin	11	3.7	2	0.2	..	....	6	1.4
Bile ducts and gallbladder	5	1.7	25	3.1	21	12.0	54	13.0
Liver	4	1.4	12	1.5	2	1.1	6	1.4
Prostate	27	9.1	44	5.5	..	....	...	....
Urinary bladder	28	9.5	27	3.4	1	0.6	9	2.2
"Ext. genitals" (Amsterdam) penis, testis, urethra (J.H.H.)	5	1.7	8	1.0	..	....	1	0.2
Ovary	..	....	...	....	17	9.7	16	3.8
Pancreas	9	3.0	18	2.2	2	1.1	12	2.9
Kidney	2	0.7	6	0.7	2	1.1	2	0.5
Lung	7	2.4	31	3.9	2	1.1	14	3.4
Mouth, etc.	17	5.7	29	3.6	..	....	3	0.7
Nose and sinuses	4	1.4	2	0.2	..	....	3	0.7
Thyroid	..	....	...	....	1	0.6	3	0.7
All other sites	7	2.4	...	....	1	0.6	...	....
Totals	296	100.2	799	99.7	175	99.8	416	99.7

hospital regarding the incidence of disease in the general population from which the hospital population is drawn.

In the colored race the broad facts stated previously as to location of primary tumors are emphasized more strongly than in the white racial group. Thus, in white males it is seen from table 9 that 50 per cent of all malignant tumors had their primary site in our class *B* (alimentary tract). But in the colored males 64 per cent of all malignant tumors fell in this organ group. In the white females 45 per cent of all malignant tumors had their primary site in some organ of the reproductive system as here defined. But in the colored females 63 per cent were so located. The racial picture afforded by table 9 suggests that the susceptibility to malignancy of the different organ systems of the body is a more diffuse and widely scattered phenomenon in the white race than it is in the colored. What cancer colored persons

have tends to appear primarily either in the alimentary tract or in the reproductive organs, and not in the other organ systems, more constantly and regularly than is the case with white people. The facts suggest that malignancy is, in certain respects, a different condition in the white race from what it is in the colored race. White people have more cancer in proportion to numbers exposed than do colored persons (as was shown in the previous paper in this series). Their malignancy is also more diffusely spread over the body, in respect of its primary site. Colored people give a different picture, both because of smaller incidence, and because of greater concentration on the two most important organ systems.

TABLE 12.—*Carcinomas of the Alimentary Tract, Liver and Pancreas. Necropsied Population.*

Location	White Males		Colored Males		White Females		Colored Females	
	Absolute Number	Per Cent	Absolute Number	Per Cent	Absolute Number	Per Cent	Absolute Number	Per Cent
Mouth (including lips and tongue)	29	14.5	4	7.0	..	....	2	12.5
Esophagus	28	14.0	1	1.8	3	3.9	1	6.25
Stomach	87	43.5	30	52.6	25	32.9	3	18.75
Intestine (including rectum)	38	19.0	10	17.5	23	30.3	6	37.5
Subtotal, alimentary tract	182	91.0	45	78.9	51	67.1	12	75.0
Liver, gallbladder and gall ducts	9	4.5	6	10.5	23	30.3	2	12.5
Pancreas	9	4.5	6	10.5	2	2.6	2	12.5
Subtotal, glandular digestive organs	18	9.0	12	21.0	25	32.9	4	25.0
Grand total	200	100.0	57	99.9	76	100.0	16	100.0

CANCER OF THE ALIMENTARY TRACT AND ASSOCIATED GLANDULAR ORGANS

From the detailed data of tables 1 to 4, table 12 has been prepared. It deals with the carcinomas of our class *B* (alimentary tract, liver and pancreas).

Unfortunately, the number of colored females in table 12 is too small to give any reliable results; hence there is no point in attempting to discuss that group on the basis of the present material.

The cases in male patients show, in this necropsied population, that the most frequent primary locus of cancer of the alimentary tract, in males, is the stomach. The intestine stands in second position in this respect, and not a particularly close second. In the white females the stomach, intestines and liver—gallbladder and gall ducts—all stand on about the same footing relative to primary location, within the group of cancers now under discussion.

The most interesting feature of the table is found in the comparison of white and colored males. In cancers of the alimentary tract in male persons the stomach is the most frequent primary site, as we have seen. But the concentration on this organ is heavier in the colored males than it is in the white males. Thus, the result obtained in the preceding section of this paper regarding cancers in general is seen to be carried along to the finer degree of specificity implied in taking the cancers of the alimentary tract by themselves. The cancers of the colored race tend to concentrate more heavily than do those of the whites, at the site of the greatest frequency.

The same tendency is shown regarding the glandular site of greatest frequency in this group of patients. While in 4.5 per cent of the

TABLE 13.—*Deaths from Cancer and Other Malignant Tumors of the Alimentary Tract, Liver and Pancreas in the General Population of the Registration Area in 1914*

Location	White Males		Colored Males		White Females		Colored Females	
	Absolute Number	Per Cent	Absolute Number	Per Cent	Absolute Number	Per Cent	Absolute Number	Per Cent
Mouth (including lips, tongue, jaw and pharynx)	1,884	12.8	40	9.9	388	2.9	16	3.8
Esophagus	465	3.2	10	2.5	124	0.9	6	1.4
Stomach	6,812	46.4	203	50.1	5,535	40.9	198	46.5
Intestine (including rectum)	2,660	18.1	49	12.1	3,414	25.2	103	24.2
Subtotal, alimentary tract	11,821	80.6	302	74.6	9,481	69.9	323	75.9
Liver, gallbladder and gall ducts	2,499	17.0	87	21.5	3,779	27.9	93	21.8
Pancreas	352	2.4	16	3.9	308	2.3	10	2.3
Subtotal, glandular digestive organs	2,851	19.4	103	25.4	4,087	30.2	103	24.1
Totals	14,672	100.0	405	100.0	13,568	100.1	426	100.0

white males the cancers of the defined group are primarily located in the gallbladder or liver, in 10.5 per cent of the colored males the primary location of the cancer is in these organs.

Let us see next whether a general population shows similar relations. Table 13 corresponds to table 12, but it relates to the general population of the Registration Area in 1914-1915. The data are compiled from table 2 of the report cited. The figures of table 13 are not precisely comparable with those of table 12, because they include all the malignant tumors, sarcomas as well as carcinomas, whereas table 12 includes carcinomas only. But for the present purpose this discrepancy in comprehensiveness will make no serious difference.

Considering the much greater uncertainty as to diagnosis implicate in the figures of table 13 as compared with those of table 12, the general broad agreement between the percentage columns of the two tables is somewhat remarkable. It certainly is not what one would expect who confined his statistical reading solely to the severe indict-

ments of official vital statistics regarding cancer, in which pathologists are perennially, and in some respects justifiably, wont to indulge.[6]

In our necropsied population 43.5 per cent of the white males with cancer in any of the locations specified in table 12, had it in the stomach. The corresponding figure from table 13 for the general population is 46.4 per cent. Similarly, in the colored males the figure for stomach cancer in the necropsied population (table 12) is 52.6 per cent, while for the general population (table 13) it is 50.1 per cent. These are not large discrepancies.

Table 13 confirms and extends the conclusions drawn from table 12 regarding racial differences in location of cancer of the alimentary tract. There is the same tendency toward more marked concentration at the most frequent site (stomach) in the negroes of both sexes, than in the whites of the same sex.

TABLE 14.—*Malignant Tumors of Primary and Secondary Reproductive Organs in Females. Necropsied Population*

Location	White Persons		Colored Persons	
	Absolute Number	Per Cent	Absolute Number	Per Cent
Ovary	21	20.0	6	12.0
Uterus	52	49.5	28	56.0
Breast	32	30.5	16	32.0
Totals	105	100.0	50	100.0

CANCER OF THE FEMALE REPRODUCTIVE ORGANS, PRIMARY AND SECONDARY

From the detailed tables 1 to 8, table 14 has been prepared. It deals with all malignant tumors of the primary and secondary organs of reproduction in the female (our class *C*).

In both races, in this necropsy experience, more than a half of the malignant growths of the primary and secondary reproductive organs have their primary site in the uterus. This is the most frequent site for this organ system as a whole. The concentration on this site of greatest frequency is higher in the negroes than in the whites, just as has been shown in previous sections of this paper to be true for malignant tumors in general, and for cancers of the alimentary tract and its associated glandular organs.

6. The latest discussion of this point is found in Wells, H. G.: Cancer Statistics as they Appear to Pathologist, J. A. M. A. **88**:199 and 476 (Feb. 5 and 12) 1927, and editorial comments concerning this article in the British Medical Journal (**1**:579 [March 26] 1927), which end as follows: "One conclusion to be drawn from his investigations is that there must be a sad ignorance of the science of statistics and of its proper mode of application."

Corresponding figures to those of table 14 are shown in table 15 for the general population of the Registration Area in 1914.[3]

Again, the tendency of the colored patients to show greater concentration of incidence on the most frequent site in the group, already observed in the necropsied population, is exhibited with even more marked intensity in the general population.

METASTASES

In following up the definite racial differences in the distribution of the sites of the primary cancers, it is desirable to examine the facts relative to secondary or metastatic growths. The individual cases have been minutely studied from this point of view and extremely detailed tables prepared to show the *locus* of each metastatic tumor, in relation to the site of the primary growth. It is unnecessary to reproduce all this detail here, particularly since when such extreme fineness of sub-

TABLE 15.—*Deaths from Cancer and other Malignant Tumors of the Ovary, Uterus and Breast in the General Population of the Registration Area, 1914*

Location	White Persons		Colored Persons	
	Absolute Number	Per Cent	Absolute Number	Per Cent
Ovary	438	3.5	13	1.7
Uterus	6,887	55.3	583	73.3
Breast	5,136	41.2	199	25.0
Totals	12,461	100.0	795	100.0

division of the material is practiced, the absolute magnitude of the whole is not sufficiently great to give significant numbers in many of the classes.

All that we shall attempt to do here is to set forth such general conclusions regarding the frequency and location of metastases as seem warranted by the data.

Table 16 shows the number of cases, by sex, color and site of the primary tumor, in which *no* secondary or metastatic tumors were found at the postmortem examination. For the sake of homogeneity, only carcinomas are included in table 16. It should be said that when this table was made, direct and continuous invasion of an organ contiguous to that in which the primary cancer occurred was not counted as metastasis. A secondary or metastatic tumor was defined for this study as one of the same cellular type, but located in a different organ or part of the body from the primary tumor, and having no continuous connection by tumor tissue with the primary growth.

From table 16 it is apparent that a larger proportion of the colored persons than of the white persons, both male and female, exhibit no secondary or metastatic cancers at necropsy. Or, to put the matter

TABLE 16—*The Number and Proportion of Cases of Carcinoma Showing no Metastases at Necropsy*

	Site of Primary Cancer	White Males			Colored Males			White Females			Colored Females		
		Total Cases with Primary Tumor at Specified Site	Number Showing No Metastases	Per Cent Showing No Metastases	Total Cases with Primary Tumor at Specified Site	Number Showing No Metastases	Per Cent Showing No Metastases	Total Cases with Primary Tumor at Specified Site	Number Showing No Metastases	Per Cent Showing No Metastases	Total Cases with Primary Tumor at Specified Site	Number Showing No Metastases	Per Cent Showing No Metastases
A.	Skin	11	4	36.36	..	..	.....	..	..	.....	1	..	.....
B-I.	Mouth	29	11	37.93	4	1	25.00	..	..	.....	2	2	100.00
B-II.	Esophagus	28	8	28.57	1	..	.....	3	3	100.00	1	..	.....
B-III.	Stomach	87	21	24.14	30	9	30.00	25	6	24.00	3	2	66.67
B-IV.	Intestines	38	10	26.32	10	6	60.00	23	11	47.83	6	4	66.67
B-V.	Liver, gallbladder and pancreas	18	3	16.67	12	3	25.00	25	6	24.00	4	2	50.00
C-I.	Gonads	1	..	.....	..	..	.....	17	2	11.76	5	2	40.00
C-II.	Copulatory organs	2	1	50.00	3	1	33.33	..	..	.....	..	..	.....
C-III.	Secondary organs	30	9	30.00	4	2	50.00	(a) 45	21	46.67	(a) 25	9	36.00
								(b) 30	5	16.67	(b) 15	3	20.00
D-I.	Kidney	2	..	.....	..	..	.....	2	1	50.00	..	..	.....
D-II.	Bladder and urethra	30	13	43.33	4	2	50.00	1	1	100.00	1	..	.....
E.	Respiratory system	13	2	15.38	7	1	14.29	2	..	.....	1	..	.....
F.	Endocrine system	4	2	50.00	..	..	.....	2	1	50.00	..	..	.....
K.	Peritoneum	3	1	33.33	..	..	.....	..	..	.....	..	..	.....
	Totals, all primary sites	296	85	28.72	75	25	33.33	175	57	32.57	64	24	37.50

the other way about, the white people in the necropsy experience of the Johns Hopkins Hospital exhibit a greater frequency of metastatic or secondary growths from their primary cancers than do the colored people. Thus, when all primary sites are taken together, 33.3 per cent of the male colored patients showed no metastases, as against 28.7 per cent of the male white patients, a difference of 4.6 ± 4.1. In the case of the females 37.5 per cent of the colored patients show no metastases as against 32.6 per cent of the white patients. Here the difference in favor of the colored people amounts to 4.9 ± 4.7 per cent. These differences are not statistically significant. At the same time the fact must not be overlooked that in every respect in which the colored have been compared with the white people regarding malignancy in this experience, there has appeared a tendency toward differentiation between the two racial groups.

The incidence of metastases in the present experience is markedly different from that recently published by Niceforo[7] based on Italian

TABLE 17.—*Number of Separate Metastatic Tumors—Carcinoma Only*

Group	Number of Separate Metastatic Tumors in the Same Person														
	0	1	2	3	4	5	6	7	8	9	10	11	12	18	No Information	Totals
Male, white	85	83	53	31	23	11	7	1	1	..	1	..	..	..	..	296
Male, colored	25	10	15	11	4	5	3	1	1	..	..	..	..	..	..	75
Female, white	57	28	30	21	17	9	3	4	2	..	..	1	1	1	1	175
Female, colored	24	10	7	3	5	4	5	1	3	2	..	..	..	..	..	64
Totals	191	131	105	66	49	29	18	7	7	2	1	1	1	1	1	610

necropsies. His table X, p. 33, shows only 11.2 per cent of male patients with malignant tumor as exhibiting metastases, and 17.8 per cent of female patients. These percentages seem unduly low. They suggest that secondary growths must have been overlooked in a good many cases.

In the necropsy experience of the Johns Hopkins Hospital it is an interesting fact that, while proportionately more of the colored patients than of the white patients are found at necropsy to have no metastatic tumors, when secondary growths do occur they are distributed more widely to different organs and tissues in the colored than in the white patients.

This fact is brought out by the data of tables 17 and 18. We have tabulated, for each case, the total number of instances of the occurrence of metastatic tumors in separate and distinct organs or tissues. From the frequency distributions of table 17 the biometric constants of table 18 have been calculated. It should be understood that the frequencies are not necessarily of separate metastatic tumors. These may be numer-

7. Niceforo, A.: Primi resultati di una inchiesta sui morti per tumori maligni in Italia, appendix to *Le Assicurazioni Sociali*, 1927, ann. III, no. 1.

ous in a single organ such as the liver or kidney. The frequencies are of *locations* of metastatic growth, which may or may not be multiple in any particular location.

From table 18 it appears that, so far as the present necropsy experience is concerned, when there are any secondary growths from a primary carcinoma, they are more widely distributed, on the average, in colored patients than in white patients. Relatively the differences are considerable. Thus, among the males the mean number of separate metastatic locations per patient is 25 per cent greater in the colored

TABLE 18.—*Biometric Constants for Number of Metastatic Tumors in Those Cases in Which any Metastases Occurred*

Group	Mean Number of Separate Metastatic Tumors in the Same Person	Standard Deviation	Coefficient of Variation
Male, white	2.35 ± 0.07	1.54 ± 0.05	65.5 ± 2.9
Male, colored	2.94 ± 0.16	1.69 ± 0.11	57.5 ± 5.0
Female, white	3.14 ± 0.15	2.44 ± 0.11	77.7 ± 5.1
Female, colored	3.80 ± 0.27	2.49 ± 0.19	65.5 ± 6.7

TABLE 19.—*Biometric Constants for Age at Death in (a) Cases Showing no Metastases, and (b) Cases with Metastases—Carcinoma Only*

	Mean Age at Death (Years)		Standard Deviation (Years)		Coefficient of Variation (Years)	
Group	Cases Without Metastases	Cases With Metastases	Cases Without Metastases	Cases With Metastases	Cases Without Metastases	Cases With Metastases
Male, white	57.48 ± 0.93	54.69 ± 0.55	12.65 ± 0.65	11.89 ± 0.39	22.0 ± 1.2	21.7 ± 0.7
Male, colored	52.04 ± 1.78	51.89 ± 1.14	13.17 ± 1.26	11.92 ± 0.80	25.3 ± 2.5	23.0 ± 1.6
Female, white	51.38 ± 1.08	50.87 ± 0.71	12.07 ± 0.73	11.37 ± 0.50	23.5 ± 1.6	22.4 ± 1.0
Female, colored	49.85 ± 1.39	47.47 ± 1.26	10.07 ± 0.98	11.83 ± 0.89	20.2 ± 2.0	24.9 ± 2.0

group than in the white group. Among the females the corresponding percentage is 21.

Table 18 also shows an interesting, an even more marked, sex difference in frequency of separate locations of metastatic tumors per patient. The average number of separate metastatic locations per person is 34 per cent higher in white women than in white men, in this experience. The corresponding percentage for the colored patients is 29.

The ages at death of the patients in this experience who exhibited secondary or metastatic growths at the time of death furnish an interesting point for comparison with those of patients who showed no such secondary tumors. Table 19 presents the biometric constants necessary for such a comparison, for carcinomatous patients only.

The outstanding result shown by the figures of table 19 is that (in necropsy experience of the Johns Hopkins Hospital) patients with

carcinoma with secondary metastatic tumors die at a younger average age than patients with similar cases but no metastatic growths at necropsy. No one of the differences between the means is significant taken separately, regard being taken of its probable error. But all four groups agree in showing the same tendency. Since these four groups represent completely independent events from the standpoint of the theory of probability there is a fairly considerable probability that the indicated trend of the mean ages at death represents a clinical reality. There is also generally less variation, both absolute and relative, in the ages at death among those patients with metastases than among those without.

The obvious suggestion in explanation of the results of table 19 is that carcinomas which metastasize are more malignant than those which do not, and on that account kill the patient sooner, and therefore at a lower average age. But this suggestion implies, of course, that the carcinomas which did metastasize and those which did not all started at the same average age of the patient. This may or may not be true. The data now available do not permit a determination of the point. It is, therefore, impossible to say definitely whether the suggested explanation of the observations is the correct one or not.

SUMMARY

In this paper there are first presented detailed tabulations showing the site of the primary tumor in the 816 cases of malignant neoplasms included in that part of the necropsy experience of the Johns Hopkins Hospital dealt with in this series of studies.

These data indicate that:

1. In males malignant tumors occur most often in the alimentary tract and its associated glandular organs, and in females in the reproductive system (primary and secondary sex organs).

2. Sarcoma and other noncarcinomatous malignant neoplasms do not exhibit any corresponding concentration of organologic location.

3. Only one case of multiple primary malignant growth occurred in the experience.

4. In this experience there is a greater concentration of the carcinoma at the most favored site in the colored race than in the white race, both in general and for cancer of the alimentary tract and the female reproductive organs separately.

5. The proportion of cases showing no secondary or metastatic tumors is somewhat higher in the colored than in the white group, in this experience, being 33 per cent for colored males against 29 for white males, and 38 per cent for colored females against 33 for white females. The samples are small, however, and the differences cannot be regarded as statistically significant.

6. In those cases in which secondary or metastatic tumors do occur, the mean number of separate locations of such secondary tumors is somewhat higher in the colored than in the white race, in this experience.

7. The results set forth in paragraphs 4, 5 and 6, together with the evidence presented in the preceding paper in this series [1] suggest that there is a difference between the white and the negro races in relation to malignant disease which manifests itself both in relative incidence and in the biologic and clinical characteristics of malignancy when present.

8. The mean age at death of persons showing metastatic tumors at necropsy is from 1 to 3 years lower than it is in persons without such secondary growths, in this experience.

LIPOID CELL SPLENOHEPATOMEGALY (NIEMANN)*

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Complete descriptions of three cases of lipoid splenohepatomegaly by Bloom and L. Pick (Niemann) have appeared in the literature within the past two years. A survey of the literature yields reports of six more cases in which the lesions described coincide with present conceptions of the pathologic process of this disease. Most cases have been confused with Gaucher's disease, because of the resemblance of the pathologic lesions. The difficulty in differentiation is mainly due to the inability to recognize the derivation of the pathologic cells. It is well known that in Gaucher's splenomegaly the cell is derived from the endothelium of the sinus wall and grows into the lumen of the sinus. In Niemann's disease, the cell is located in the pulp and is rarely found within the sinus. The clarity with which the location of the peculiar cells characteristic of this disease was demonstrated, and certain peculiar staining reactions found, justifies a detailed pathologic record of the case to be described. A complete clinical report with a survey of the literature by B. Kramer will appear shortly in the *Medical Clinics of North America*.

PATHOLOGIC REPORT OF A CASE

The spleen was removed by operation. Forty-eight hours later, the child developed diphtheria, was removed to another hospital and died. Necropsy was unobtainable. At the operating table, the surgeon was requested to leave the pedicle clamps in situ, and the spleen was taken at once to the laboratory where a small thin piece was removed for rapid examination. The organ was placed in 10 per cent formaldehyde solution for several weeks. Sections were then removed for further study.

The spleen weighed 480 Gm.; the normal shape was preserved. The surface appeared corrugated and yellow. Scattered over the surface were many bright red irregular spots and a few small pearly white patches varying in size from 1 to 2 mm. The consistency was firm. There were no accompanying lymph nodes.

On section, the cut surface was grayish pink and contained many scattered circular areas varying in size up to 2 mm. in diameter. These areas were red and had a gray center. The appearance was homogeneous and similar throughout; there were no nodules or infarctions.

Microscopically, the specimen could not be recognized as splenic tissue. All fields showed an alveolar arrangement of collections of large cells. Here and there were occasional groups of small round cells, varying in size, and containing in their substance one and sometimes two arterioles, obviously atrophied follicles. Many of the large cells had encroached on the structure of the follicles, and in some places the previous location of the latter could be detected only by a few surviving lymphocytes and the central arteriole. This encroachment was mani-

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fested either by a sharp boundary line between the masses of large cells, with a diminution in the size of the follicles, or by a gradual merging of an irregular line of large cells into it. No vestige of follicular reticulum could be demonstrated in the sites of the destroyed follicles. The larger follicles contained varying numbers of large cells filled with coarse granules.

In specimens from that portion of the spleen which was fixed en masse, spaces were seen between the alveoli, the appearance resembling cracks in the section due to heavy pressure on the cover glass (fig. 1). These spaces, however, were

Fig. 1.—Dilated venous sinuses, mostly empty, after en masse fixation of spleen; × 110.

not artefacts, but were the lumina of dilated venous sinuses, which in many instances showed greatly thickened walls. The sinuses stood out prominently and clearly and contained a few cells, but practically no blood. In specimens examined before prolonged fixation, the sinus walls were collapsed and thus obliterated the lumen. The picture produced was one of complete solidity. The alveoli varied in size and shape, but all were packed solidly with cells. In the center of some, there was a clump of reticulum from which the large cells appeared to radiate. The walls of the alveoli for the most part consisted of a fine reticulum

which could be traced to the sinus walls. With the Mallory aniline blue stain, the structure of the sinus wall stood out clearly, and the fibrils could be traced into and around the alveoli, but it apparently did not form a reticulum in the alveolus (fig. 2). The fibrils appeared as single strands penetrating into the alveolus between the large cells.

The sinus walls consisted of several layers of fibrils loosely bound together. The lumena of the sinuses were lined with either flat or cuboidal cells. The flat cells resembled those found in the normal splenic sinus. They were long, spindle-shaped, with clear staining cytoplasm, and they occurred in single layers.

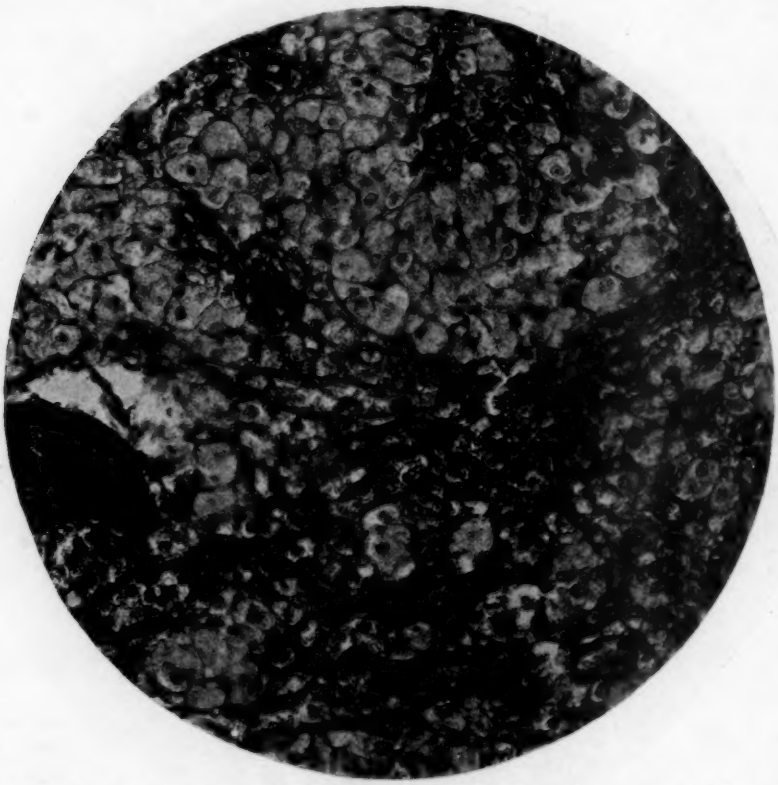

Fig. 2.—Distribution of reticulum. Mallory aniline blue stain; × 300.

The nuclei were long and oval; they stained pale blue, showed a clear chromatic network, and bulged into the sinus, beyond the limits of the enclosing protoplasm. The cuboidal cells were arranged in single rows. In some instances, they lay in close contact with one another, while in others they stood out individually. The cytoplasm appeared homogeneous and stained deeply with eosin. The nucleus was about the size of a lymphocyte and stained opaquely; it was situated in the center of the cell.

The sinuses contained a moderate number of lymphocytes; some contained a few red blood cells and occasionally a large cell like those seen in the pulp. In no instance could a large cell be found attached to the internal sinus wall. By far, most of the sinuses in that portion studied after ligation and prolonged

fixation were dilated, while in the sections studied immediately after removal, the sinus walls were collapsed and their lumena obliterated. The sinuses varied much in size, and their normal anatomy could scarcely be recognized.

Between the sinuses lay groups of large cells measuring up to 50 microns; these occupied the entire pulp. No reticulum fiber could be demonstrated, except those derived from the sinus walls. The cells were polygonal and were packed closely together forming one solid mass, without central or peripheral spaces, except where they bordered on the walls of the dilated sinus. The cell membranes stood out clearly; the cytoplasm appeared granular, and this appearance was preserved with most fixatives and stains. The granules were packed closely and appeared spherical and refractile; in some sections, this appearance resembled a fine abundant reticulum in the cytoplasm. The behavior of this cytoplasmic substance to stains, however, proved it to be granular. The granules were not soluble in the usual fat solvents, i. e., alcohol and xylol, but reached positively with most lipoid reagents. In all material fixed in paraffin, they were demonstrable;

Reactions of Granules to Lipoid Reagents and Stains

Fixative	Mordant	Stain	Color of Granules
Formaldehyde paraffin....	0	Hematoxyln eosin.....	Lavendar
Formaldehyde paraffin....	0	Weigert iron Hematoxyln ($NoNH_4$)	Pale gray
Formaldehyde paraffin....	0	Weigert iron Hematoxyln (NH_4)...	Blue gray
Formaldehyde paraffin....	0	Nile blue sulphate.....	Pale blue
Formaldehyde frozen.....	0	Scarlet R.....	Gray, occasionally gold yellow
Formaldehyde frozen.....	Potassium bichromate	Lorrain Smith-Dietrich.....	Yellow gray
Formaldehyde frozen.....	.	Marchi	Unstained
Helley paraffin....	0	Van Giesen-Harris Hematoxyln.....	Pale yellow
Helley paraffin....	0	Van Giesen weigert iron.....	Dark brown
Helley paraffin....	0	Mallory aniline blue.....	Blue
Formaldehyde-Ciaccio.....	Potassium bichromate	Hematoxyln	Orange

in not one cell had there been even a suggestion of vacuolization. The reactions of the granules to lipoid reagents and strains are shown in the table.

The stains were repeated on various portions of spleen at different periods, and the results were uniform. The results indicate the lipoidal nature of the granules and the complete absence of free fat. The well known inconsistency of results with lipoid reagents may account for the negative outcome with the nile blue sulphate.

With the Ciaccio method, a striking picture was obtained (fig. 3). Although the reaction was definitely positive, the distributions of orange granule-bearing cells was not diffuse, and in its irregularity seemed to follow a definite system. According to the quantity of granules and their intensity of color, the cells could be divided into four groups.

(1) Those scattered throughout the pulp, in which the granules were fine, evenly distributed, and stained either not at all, or so faintly that no color could be detected. This type of cell predominated.

(2) Cells similar to the foregoing cells, within which the granules stained an unmistakable golden yellow. These cells were scattered about irregularly and occurred either singly or in groups of small numbers.

(3) Cells in which the granules stained deeply, were packed more closely and of irregular size. These cells were found at the borders of the lymph follicles, and about the central clump of reticulum which was seen about the alveoli.

(4) Cells situated in the bodies of the follicles, which contained an enormous amount of deeply staining golden red and dark, irregular granules, which were not as refractile as those observed in the foregoing cells. A study of these cells revealed the fact that although pigmented bodies were found in them, with practically all stains, their number was seen to be far greater with lipoidal reagents.

Fig. 3.—Distribution and character of granules. Ciaccio stain; × 300. Note the heavy accumulation of pigment and granules in cells in the upper part of the picture.

With nonlipoidal stains, they appeared as large coarse granules with a reddish brown color, resembling lipofuchsin, and the enclosing clear protoplasm was plainly visible. Evidently these cells were the usual intrafollicular macrophages, filled with lipoid and pigment.

Staining for iron yielded unsatisfactory results with the berlin blue, prussian blue, Turnbull and Mallory methods. Although rarely a cell containing a few blue pigment granules was found, the reaction could not be accepted as positive.

The nuclei were situated eccentrically for the most part. They occurred singly. In an occasional cell, two or more nuclei might be found. They were small in comparison to the size of the cell, and were uniformly about 6 microns in diameter. They were spherical and contained a small nucleus with a definite chromatic network.

In most respects, the microscopic changes coincide with those described as occurring in Niemann's splenomegaly. The presence of the characteristic lipoid-bearing cell, the absence of demonstrable iron, and the most important characteristic, the absence of pathologic cells in the splenic sinuses, distinguish the condition from Gaucher's disease. Certain minor differences from lipoid histiocytosis are noted, i. e., in the complete absence of vacuolization and the negative results with certain lipoidal reagents, as, for instance, the nile blue sulphate reaction. The great difference from previous experiences as reported is the insolubility of the granules in fat solvents. This point, emphasized by Bloom, is absent in this case. Evidently in his cases he was dealing with soluble lipoids, while in this case the lipoid is insoluble.

From the standpoint of histologic study, the difference in appearance between the sections obtained by fixation of a freshly excised portion of spleen and those after en masse fixation cannot be over emphasized. The location of the predominating cells was unmistakably identified as being in the pulp and not in the sinuses, thus fulfilling the most important requirement in the diagnosis of Niemann's splenomegaly.

Laboratory Methods and Technical Notes

IDENTIFICATION OF HUMAN SEMINAL STAINS

Precipitin Reaction of Seminal Fluid *

LUDVIG HEKTOEN, M.D., AND GEORGE J. RUKSTINAT, M.D., CHICAGO

It has been found that the injection of rabbits with the semen of man, swine, bull or horse induces the formation of specific precipitins for the homologous fluid.[1] In most cases, precipitins develop also for the homologous blood serum. The extracts of human spermatozoa in salt solution appear to give the same result as the seminal fluid. The precipitins for blood serums in antisemen serum may be removed completely by selective absorption with an equal quantity of a 1:200 dilution of the corresponding serum. The seminal precipitin reaction reveals the presence in semen of a substance or substances peculiar to it, and consequently the reaction may be of value in studying the nature of suspected spots and stains.

STAINING HUMAN SPERMATOZOA DEPOSITED ON CLOTH

About twenty years ago, a number of articles appeared on methods and suggestions for staining spermatozoa on cloth. The underlying principles in all the methods involve, first, the solvent action of an alkali on the dried secretion and, second, the staining of spermatozoa. To these have been added, at times, fixatives to preserve the tails, complex stains to demonstrate the various components of the cell in different colors and refinements to render fibers of cloth colorless or nearly so.

Hankin [2] elaborated a method for warm climates where intense drying and putrefactive changes occur quickly. Tannin and boiling water are used as cellular fixatives, sulphuric acid, potassium bichromate and potassium cyanide are employed as solvents, while gentian violet is used for staining the sperm. Windsor,[3] working in warm climates, finds it better to fix the cloth in Müller's solution, loosen the spermatozoa by

* From the John McCormick Institute for Infectious Diseases and the Norman Bridge Pathological Laboratory, Rush Medical College.

1. Farnum, C. G.: The Biologic Test for Semen, J. A. M. A. **37**:1721 (Dec. 28) 1901; Tr. Chicago Path. Soc. **5**:31, 1901. Strube, G.: Deutsche med. Wchnschr. **28**:425, 1902. Pfeiffer, H.: Wien. med. Wchnschr. **18**:637, 1905. Dervieux, M.: Compt. rend. Acad. d. sc. **172**:1384, 1921. Hektoen, Ludvig: Specific Precipitin Test for Human Semen, J. A. M. A. **78**:704 (March 11) 1922. Hektoen, Ludvig, and Manly, Leonard S.: J. Infect. Dis. **32**:167, 1923.
2. Hankin, E. H.: Brit. M. J. **2**:1261, 1843, 1906.
3. Windsor, F. N.: Brit. M. J. **2**:501, 1908.

pressing the cloth against glass and squeezing the sperm-laden solution onto a slide; and then to stain this film, free from all dirt and fibers of cloth with eosin. Ellermann,[4] whose method is, in many respects, closely followed in the present report, uses a combination of erythrosin and Weigert's iron-hematoxylin stains, and claims that the fibers of cloth remain unstained. The latter contention is disputed by Baecchi [5] who evolved a process in which acid fuchsin and methyl blue are used as stains and in which destaining is carried out in acid alcohol.

Spermatozoon from seminal stain on cloth; × 1,000.

The method we describe makes use of Mallory and Wright's chloride of iron hematoxylin stain.[6]

1. Soak the stained cloth in 1 per cent ammonium hydroxide solution in water for from twelve to twenty-four hours.

2. Select a single thread and stain two minutes in 5 per cent aqueous solution of erythrosin.

3. Wash quickly in distilled water.

4. Stain with 10 per cent aqueous solution of ferric chloride two minutes.

5. Transfer directly to 2 per cent aqueous solution of hematoxylin for two minutes.

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4. Ellermann, V.: Vrtljschr. f. gerichtl. Med. **42**:116, 1911.

5. Baecchi, B.: Vrtljschr. f. gerichtl. Med. **43**:1, 1912.

6. Mallory, F., and Wright, J.: Pathological Technique, Philadelphia, W. B. Saunders Company, 1924, p. 96.

6. Wash quickly in distilled water.

7. Transfer to 0.5 per cent aqueous ferric chloride and tease out fiber to its finest shreds. Remove from this solution when threads are reddish pink or light brown.

8. Wash in distilled water quickly.

9. Dehydrate in absolute alcohol.

10. Clear in creosote.

11. Mount in balsam.

Better results are obtained if the differentiation is carried out slowly in 0.5 per cent ferric chloride solution than in stronger solutions. Boiling the cloth for one minute in water after soaking in ammonia solution helps preserve the tails. When the stain takes well, the head of the spermatozoon is from a dark purple to black in the posterior two-thirds, while the anterior third is pink, and the tail is from a pink to lavender. The connecting piece frequently is evident. The threads of the cloth may stain more or less pinkish.

Precipitin Tests for Human Semen and Demonstrations of Spermatozoa

Materials Tested		Precipitin Serum of Rabbits Injected with Human Semen: Untreated*	Precipitin Serum of Rabbits Injected with Human Semen: After Absorption with Equal Parts of Human Serum 1:100	Precipitin Serum of Rabbits Injected with Human Serum	Spermatozoa Found
Extracts in salt solution of suspected seminal stains on cloths	1	+	+	+	+
	2	+	+	+	+ (fig.)
	3	+	+	+	+
	4	+	+	+	+
	5	+	+	+	+
	6	+	+	+	+
	7	0	0	0	0
	8	0	0	0	0
Human seminal fluid		1,000	1,000	20+	
Human serum		20	0	10,000	

* + = positive precipitin reaction; 0 = no reaction with precipitin serums. The figures give the highest dilution of seminal fluid and serum that gave precipitates after contact for one hour with precipitin serum at room temperature.

The results of recent examinations of suspected stains with the method just described for staining spermatozoa on cloth and with the precipitin test are given in the table. The precipitin tests were made with the perfectly clear extracts of the suspected spot in salt solution, care being taken to use relatively small amounts of salt solution in order to obtain as strong extracts as possible. The tests were made by the contact or layer method, and the results were read after one hour at the room temperature.

While question as to the source of the stain need not arise if spermatozoa are found, it is obvious that the precipitin test may be of help in identifying seminal stains.

In connection with this matter it is of interest to refer to Landsteiner and Levene's demonstration of iso-agglutinative group substances in spermatozoa.[7] They found that spermatozoa from persons belonging to blood groups A or B absorb specifically the agglutinins for the red cells

7. Landsteiner and Levene: J. Immunol. **12**:415, 1926.

of these groups. This fact at once suggests that it may be possible to trace seminal stains to persons of certain blood groups. For example, group 0 serum absorbed with seminal stains on cloth for one hour at room temperature and in the box over night lost agglutinin A. The man in question belonged to group A. In such tests, it is necessary to make control tests with the unstained cloth because in some cases the cloth itself absorbs the agglutinin.

METHOD OF MAKING REPEATED DETERMINATIONS OF THE INTRA-ARTERIAL SYSTOLIC BLOOD PRESSURE IN DOGS*

CLYDE R. JENSEN, M.D., AND CARL W. APFELBACH, M.D., CHICAGO

The need of a reliable method for making determinations of blood pressure in unanesthetized animals used in experimental work has led to the development of various methods, some of which have been described recently by Allen.[1] Several "bloodless" methods, employing cuffs to fit the tapering extremities of dogs have been used, and, according to the authors, reliable results were obtained (Janeway,[2] Kolls[3] and Allen[1]). It has been our experience that the variables associated with the cuff methods make the results untrustworthy. Some of the variables are: inability to govern the tonus of the muscles of the legs; shivering; difficulty in applying the cuff in the same place and in the same way each time, and inconstancy in the selection of the correct systolic impulse below the cuff.

The method adopted by us and described herein is not new. In 1878, Pavlov[4] introduced a cannula into a small artery of a dog's leg without anesthesia. Needles and fine capillary glass pipets have been inserted into capillaries and small arterioles, and the measurement of capillary and blood pressures determined by water and mercury manometers. However, such methods are not in general use in experimental work on dogs, the more cumbersome cuff methods being employed generally.

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* From the Pathological Laboratory of the Presbyterian Hospital and the Norman Bridge Pathological Laboratory of Rush Medical College.

* Aided by Grant no. 113 from the Committee on Scientific Research of the American Medical Association.

1. Allen, F. M.: Auscultatory Estimation of the Blood Pressure of Dogs, J. Metab. Research **4**:431, 1923.

2. Janeway, T. C.: A Modification of the Riva-Rocci Method of Determining Blood-Pressure for Use on the Dog, Proc. Soc. Exper. Biol. & Med. **6**:108-109, 1909.

3. Kolls, A. C.: An Indirect Method for the Determination of Blood Pressure in the Unanesthetized Dog, J. Pharmacol. & Exper. Therap. **15**:443-452, 1920.

4. Pavlov, J.: Ueber die normalen Blutdruckschwankungen beim Hunde, Arch, f. d. ges. Physiol. **20**:215, 1879-1880.

We introduce into the femoral artery a 22 or 24 gage needle, attached to a mercury manometer by a glass Luer adapter and rubber tube. The mercury manometer (fig. 1) is a U-shaped tube, with a bore of 1 or 2 mm., mounted on the front of a rectangular box that is open at the top and back. The side-arm that connects with the needle is at a level approximately the same as that of the femoral artery of a dog tied to an operating board. At the upper end of the same arm of the U-tube there is a stopcock, the latter joining the U-tube with a bottle (fig. 2) containing a 2 per cent solution of sodium citrate. This solution is pumped from this bottle into the U-tube above the mercury and out through the needle. A metric scale is mounted on a movable slide along one side of the U-tube.

Bleeding from the artery is controlled by digital pressure in three or four minutes. It has been used daily on the same dogs for several weeks without

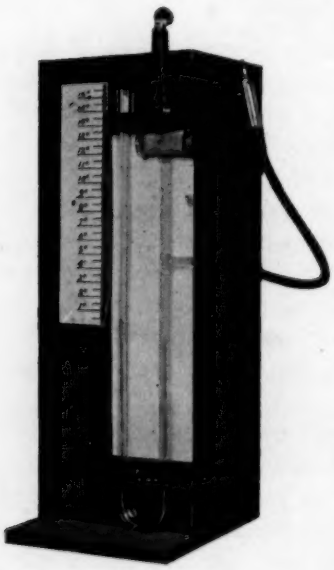

Figure 1

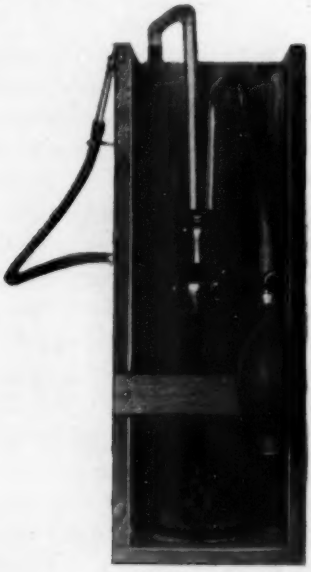

Figure 2

Fig. 1.—Mercury manometer.

Fig. 2.—Stopcock joining U-tube with bottle containing 2 per cent solution of sodium citrate.

local alterations that interfere with the dog's health. The majority of dogs are not excited when strapped to a board if they have been treated gently for about one week. Before the needle is introduced in the femoral artery, the dog is allowed to relax. A sharp needle is used to diminish pain and also to allow rapid and easy entrance into the tough wall of the artery.

We have used manometers with 1 and 2 mm. bores. The estimation of the pressure in each is approximately the same, the chief difference being the degree of oscillation associated with respiration, and the intra-arterial fluctuation of systole and diastole. The results obtained from two manometers connected with the same artery, one through a 1 mm. cannula and one through a 22 gage needle, are given in the table.

The average systolic pressure is estimated by taking the mean of the maximum and minimum fluctuations associated with respiration.

With cessation of respiration, which removes the large fluctuations in the manometer connected with the cannula, and with progressive fall in blood pressure preceding death, the mercury level in the two manometers falls at the same rate and is at same levels at any instant.

SUMMARY

The systolic blood pressure obtained by the apparatus described, a 22 gage needle being used, is usually from 2 to 4 mm. lower than the estimation made simultaneously in the same artery through a 1 mm. cannula.

Results Obtained with Two Manometers

Cannula in left femoral artery	22 gage needle in left femoral artery
156 mm.	153 mm.
149 mm.	145 mm.
108 mm.	104 mm.

We believe that there are fewer variables in this method than in the cuff methods.

The apparatus is compact and easily manipulated, and in the dog it is a simple procedure to introduce a 22 gage needle into the femoral artery immediately distal to Poupart's ligament.

In our experience, a dog accustomed to being tied to a board is not noticeably disturbed by the needle puncture.

We presume that this method may be used in obtaining the intracardiac pressure of smaller laboratory animals, because the intra-arterial pressure obtained through a 26 gage needle is accurate, the only disadvantage being that clotting of blood in the lumen of such a needle occurs much more rapidly than with a 22 or 24 gage needle.

General Review

DIABETES INSIPIDUS

A CLINICAL REVIEW AND ANALYSIS OF NECROPSY REPORTS *

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CHICAGO

Diabetes insipidus is a clinical syndrome, the outstanding symptoms of which are polyuria and polydipsia. It was first clearly differentiated from diabetes mellitus by Willis [1] in 1670, and later by Cullen [2] in 1789. Johann Peter Frank,[3] in 1794, defined diabetes insipidus as a long continued increased secretion of a tasteless urine, and believed that it was not due to a disturbance in the function of the kidneys. A distinction is frequently made between primary, or essential, and secondary, or symptomatic, polyuria. In the primary variety, polydipsia and polyuria are the chief clinical symptoms; in the secondary variety, these symptoms constitute only part of the clinical picture, which is that of some organic disease of the brain. It is now recognized that all permanent polyurias of extrarenal origin are due to an intracranial lesion. Primary diabetes insipidus must be extremely rare (Rowntree [4]).

The enormous literature and tremendous amount of clinical and experimental work devoted to diabetes insipidus are in marked contrast to its infrequency, and tend to confirm the aphorism that things which are rare and obscure often excite the greatest interest. R. Fitz,[5] in an analysis of the statistics of two European clinics and the Johns Hopkins Hospital and Dispensary, gave an incidence of fourteen per hundred thousand patients treated. Rowntree,[4] at the Mayo Clinic, reported ten and sixteen per hundred thousand, respectively, in two series of cases; including other cases in the literature, this incidence is reduced to seven. Rabinowitch [6] found one case in 50,000 patients admitted to the Montreal General Hospital. Statistics in general indicate that diabetes insipidus is found in about 0.01 per cent of all patients treated.

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* From the Department of Pathology, University of Chicago, and the Department of Pathology and Bacteriology, Chicago College of Dental Surgery.

1. Willis: De Diusinimia, Opus Omnia, Amsterdam, 1682, sec. IV, cap. III.

2. Cullen, W.: Anfangsgründe der praktischen Arzneikunst, Leipsig, Uebers, 1789, p. 566.

3. Frank, J. P.: De curandis hominis morbis, Ordo; Genus II (diabetes), Florence, 1832.

4. Rowntree, L. G.: M. Clin. N. Amer. **5**:439, 1921; Diabetes Insipidus, J. A. M. A. **83**:399 (Aug. 9) 1924.

5. Fitz, R.: A Case of Diabetes Insipidus, Arch. Int. Med. **14**:706 (Nov.) 1914.

6. Rabinowitch, I. M.: Metabolic Studies on a Case of Diabetes Insipidus, Arch. Int. Med. **28**:355 (Sept.) 1921.

ETIOLOGY

The disease is slightly more common in males than in females, and usually occurs in persons under 40 years of age. It is not uncommonly observed in children, and, according to Külz,[7] is more likely to affect boys than girls. Occasionally, more than one member of a family is affected. Weil [8] found seventeen cases in three generations of one family. Such occurrences are probably accidental, since a true hereditary tendency has never been demonstrated.

Temporary polyuria occurs in functional nervous disorders, such as hysteria, conditions of severe emotional stress and attacks of migrane and epilepsy. Severe fright has been given as the exciting factor in cases of true diabetes insipidus (Rowntree, Oppenheim). Polyuria is occasionally encountered in pregnancy. Novak [9] reported a remarkable case of severe polydipsia and polyuria following pregnancy, which was markedly relieved, but did not completely disappear, after childbirth, and recurred with each subsequent pregnancy. These exacerbations were so characteristic that the patient was able to diagnose her condition whenever excessive thirst developed.

It is a clinical observation of long standing that polyuria frequently follows injuries of the base of the skull. These may be traumatic fractures, accidental or suicidal gunshot wounds and bayonet thrusts through the eyeball. Polyuria is most common following injuries of the posterior cranial fossa. Of twenty-six cases of traumatic polyuria collected by Kahler,[10] thirteen were due to basal skull fracture. Six were in the temporal region, four were in the posterior fossa and in only three was there commotio cerebri without fracture.

Syphilitic basal meningitis as a cause of diabetes insipidus was first emphasized by Oppenheim,[11] although its frequent occurrence in syphilitic persons was noted by Fournier. Of thirty-six patients observed by Oppenheim in whom a diagnosis of syphilitic meningitis was made, twelve had polydipsia and polyuria.

In the rare instances of tuberculous meningitis with nodular tubercles in the midbrain, polyuria may be the only symptom.

Diabetes insipidus may appear during convalescence from any of the acute infectious diseases such as measles, an instance of which was reported recently by Thompson, Keegan and Dunn.[12] In the last few

7. Külz: Handbuch der Kinderkrankheiten, Erste Hälfte, 1878, vol. 3, p. 285.
8. Weil: Virchows Arch. f. path. Anat. **115**:70, 1884.
9. Novak: Berl. klin. Wchnschr. **54**:107, 1917.
10. Kahler: Ztschr. f. Heilk. **7**:105, 1886.
11. Oppenheim: in Nothnagel: Die Syphilitischen erkrankungen des Gehirns, Speziellen Pathologie und Therapie, Vienna, 1896, vol. 9, p. 53.
12. Thompson, C. Q.; Keegan, J. J., and Dunn, A. D.: Defects of Membranous Bones, Exophthalmos and Diabetes Insipidus, Arch. Int. Med. **36**:650 (Nov.) 1925.

years diabetes insipidus has been reported with increasing frequency following epidemic encephalitis (Hall, Hoke).[13]

Persistent polyuria has been most frequently observed in association with tumors of the midbrain, and not uncommonly with dystrophia-adiposogenitalis. Strada [14] collected thirty-two tumors of the hypophysis with adiposity, in four of which polyuria was recorded in the history, and von Frankl-Hochwart [15] found seven cases of diabetes insipidus in ninety-seven instances of hypophyseal tumors without acromegaly. Polyuria has been observed in congenital tumors of the hypophysis (Erdheim), primary tumors in the region of the third ventricle and metastatic carcinomas in the posterior lobe of the hypophysis (Simmonds), gliomas of the optic chiasm (Martin and Cushing) and pinealomas (von Gierke, Horrax and Bailey). Polyuria is rarely a prominent symptom of acromegaly.

SYMPTOMS

The onset of diabetes insipidus may be sudden, as in the cases following trauma and fright, or more gradual when associated with slow-growing tumors. Of the fifteen studied by Weir, Larson and Rowntree,[16] it was definitely determined that there was a sudden onset of thirst in three. As a rule, the course is chronic, and it commonly lasts for years. The condition may be temporarily abated during acute fever. Of the syphilitic variety, Oppenheim says that the symptom of thirst in common with others of cerebral syphilis is characterized by its inconstancy. The polydipsia and polyuria may disappear for days and weeks or may appear only periodically; they may appear in any phase of the disease and may outlast all other symptoms. The disease is not primarily fatal.

The classic symptoms of diabetes insipidus are permanent polydipsia and polyuria, with the excretion of a sugar free watery urine. The question whether the polydipsia or polyuria is primary is not of great moment, except possibly in the theoretical consideration of a primary thirst center.

Numerous clinical studies have been made of diabetes insipidus. These have brought out a number of fact but have led to a great many speculations. Some writers have rightly termed it a disease of theories. The volume of urine in diabetes insipidus varies from a slight increase above the normal to enormous quantities in twenty-four hours. It is

13. Hall, G. W.: Am. J. M. Sc. **165**:551, 1923. Hoke, E.: Wien. klin. Wchnschr. **33**:562, 1920.

14. Strada, F.: Virchows Arch. f. path. Anat. **203**:1, 1911.

15. Von Frankl-Hochwart, L.: Wien. med. Wchnschr. **59**:2326, 1909.

16. Weir, J. F.; Larson, E. E., and Rowntree, L. G.: Diabetes Insipidus, Water Balance and Water Intoxication, Arch. Int. Med. **29**:306 (March) 1922.

pale, of low specific gravity and poor in salts, as indicated by freezing-point determinations. The ordinary tests of renal function do not usually show any deviation from the normal, in uncomplicated cases. The polydipsia varies with the polyuria. Rowntree [4] noted dryness of the mouth, thick and tenacious mucus, a harsh, dry skin and constipation among the distressing symptoms closely related to polyuria.

PATHOLOGIC PHYSIOLOGY

Complete agreement regarding the pathologic physiology of diabetes insipidus has not been reached. The idea that the kidneys have lost their concentrating capacity has been largely abandoned (Meyer and Meyer-Bisch).[17] Kenneway and Mottram [18] found that the concentration of chlorides in the urine was one and one-half times less than normal, being eighteen times as dilute in the urine as in the plasma. There was only four times as much urea in the urine as in the blood, or a reduction of one-fifteenth below the normal. In four cases studied by Allen and Sherrill,[19] the plasma chloride was slightly above normal in two cases, although it was low in a third. The red cell volume was high in all persons examined, while the hemoglobin content and red cell counts were comparatively low.

On the basis of careful metabolic studies, Veil [20] distinguished two types of diabetes insipidus. One was characterized by hyperosmosis of the blood and hyperchloremia; marked lability of the water balance with an exceptional exhaustion of the total water in the thirst experiment; lability of the sodium chloride balance, a slight reaction to theocin, marked response to pituitary extract and the good effect of a diet poor in chlorides; a concentrating capacity always below normal in the polyuric urine, but variable in the thirst experiment, and approaching normal after the administration of pituitary extract only when water is almost withheld. In the other, there was a tendency toward hyposmosis of the blood; a tendency toward hypochloremia; a stabile quasifixed water balance; the maintenance of water balance in the thirst experiment even to diminution of external water excretion and water retention; a relatively normal sodium chloride balance or tendency to hyperchloremia; a marked reaction to theocin, almost complete absence of a reaction to pituitary extract and therapeutic inactivity of pituitary extract; therapeutic inactivity of a diet free from sodium chloride and a concentration limit below normal of the polyuric urine which varies markedly in the thirst experiment and at different times in the same patient.

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17. Meyer, E., and Meyer-Bisch, R.: Deutsches Arch. f. klin. Med. **137**:225, 1921.
18. Kenneway, E. L., and Mottram, J. C.: Quart. J. Med. **12**:226, 1918-1919.
19. Allen and Sherrill: J. Metab. Research **3**:479, 1923.
20. Veil, W. H.: Biochem. Ztschr. **91**:317, 1918.

Observations indicate that the hyposmosis is not confined to the blood but depends on the flux from the tissues and lymph toward the blood, as can be shown by increasing the amount of sodium chloride in the diet. Possibly the condition is due to an anomaly of the tissue. The entire organism seems to be adjusted to a lower level of osmotic pressure which is the starting point of the diabetes insipidus. It may reasonably be assumed that the water exchange is so great because the level of molecular concentration in the cells is lowered. An associated condition of both forms of diabetes insipidus is a definitely recognizable reduction in the concentration of the urine. A specific gravity of from 1.016 to 1.018 is not evidence against a lowered concentration, if in normal persons under the same circumstances, there may be a variation from 1.026 to 1.030. The fundamental cause is a change in the physical and chemical nature of the substrate on which the kidneys act, namely, the tissue juices and the blood. The assumption of a functional renal disturbance, in the old sense, is hardly a satisfactory explanation. Veil believed that there is a general disturbance, the location of which, while only partly understood, must consist of a metabolic disturbance in the tissues. The question is how the hypothetic condition of water absorption by the tissues, with hyperchloremia in the one case and hyposmosis in the other, occurs. What conditions and particular influences regulate the mineral metabolism of the cells? To what extent is it controlled by the nervous system; what is the influence of the internal secretions? According to clinical observation, both factors play a definite rôle. On a purely biologic basis, it seems probable that there is a dysregulation of mineral metabolism, and that there is a centralization of this regulation which is not controlled by the kidneys alone.

Leschke [21] gave the following summary of his extensive clinical studies of diabetes insipidus:

> The important factors are pathologic increase in water excretion coincident with lowering of the normal concentrating capacity of the kidneys. This disturbance in concentrating capacity varies in different cases and is not absolute. It varies in the following ways:
>
> 1. Additions of salt and urea are quantitatively excreted within the same time as in normal persons, but with an increased volume of urine. In normal persons and in others with polyuria (nervous, convalescent) there is an increase in the concentration of the urine. In diabetes insipidus there is a measurable increase in the concentration of the added substances, but the total concentration of the urine remains almost unchanged.
>
> 2. In diabetes insipidus there is neither tachyuria nor bradyuria. The volume of water excreted depends on the amount of salt to be eliminated. Other things being equal, ingested water is excreted as rapidly as it is in healthy persons.
>
> 3. Foreign substances (potassium iodide, lactose, sodium ferrocyanide) are quantitatively as rapidly excreted as they are in normal persons. This occurs in lower concentration, dependent on the larger amount of water needed.

21. Leschke, Erich: Ztschr. f. klin. Med. **87**:901, 1919.

4. The inability to concentrate is best shown by the thirst experiment. In normal persons, the urine reaches a specific gravity of 1.030 when water is withheld. In patients with diabetes insipidus, it rarely rises above 1.010. Because of the patient's inability to excrete salts, there is a retention in the blood. Symptoms of uremia develop, characterized clinically by severe thirst, headache, loss of consciousness, restlessness, slowing of the pulse rate, dyspnea and a feeling of warmth. Chemical study of the blood shows a rise in the rest nitrogen, a lowering of the freezing point and a concentration of salt and urea.

5. The polyuria in diabetes insipidus, as in normal thirst, depends on stimulation of the renal cortex by the increased concentration of salts. The intravenous injection of concentrated salt solution, even after injury of the nerves of taste, leads to immediate thirst.

6. The inability to concentrate has not the character of an organic lesion, but is more like a functional disturbance. During febrile conditions there is a marked rise in the concentration and a diminution in the quantity of the urine, particularly during the first few days. The urine does not reach the normal concentration. In long continued fevers, the diabetes insipidus returns.

PATHOLOGIC ANATOMY

The pathologic lesions held responsible for diabetes insipidus divide themselves into three distinct types, depending on prevailing theories and the experimental production of polyuria. The first period was influenced by Claude Bernard's [22] classic experiment in which he demonstrated that piqûre of the corpus restiforme in the floor of the fourth ventricle was followed by polyuria. The same result was obtained by Eckhard [23] by means of injury to the pons and cerebellum. As a matter of fact, according to Kahler,[24] there is not any region of the midbrain, the pons, medulla or cerebellum, a lesion of which may either produce polyuria or fail to produce it. Gross pathologic lesions of the brain, particularly in the region about the fourth ventricle, were especially sought, and microscopic descriptions are conspicuously lacking.

The second period may be termed the hypophyseal period, and it had its origin in a paper by Frank [25] in which he directed attention to the frequent association of diabetes insipidus with signs of hypophyseal lesion. Frank emphasized the fact that the classic symptom of pressure arising in the hypophysis or its immediate vicinity is bitemporal hemianopia caused by pressure on the optic chiasm, and stated that it was remarkable that two such rare symptoms as bitemporal hemianopia and polyuria should frequently occur together. Kruse,[26] in 1894, observed polyuria in seven of thirty-four patients with bitemporal hemianopia,

22. Bernard, Claude: Leçons sur les propietés physiologiques et les alterations pathologiques des liquidea de l'organisme, Paris, 1859, vol. 2.
23. Eckhard: Beitr. z. Anat. u. Physiol. **4**:1, 1869; ibid. **6**:55, 1872.
24. Kahler: Ztschr. f. Heilk. **7**:105, 1886.
25. Frank, E.: Berl. klin. Wchnschr. **49**:393, 1912.
26. Kruse: Inaug. Diss., Marburg, 1894.

while Spanbock and Steinhaus [27] found it eleven times in fifty patients. Interest was thus centered on the hypophysis, other lesions being accorded secondary importance, and when gross lesions were absent, it was maintained that pressure on the hypophysis by distant lesions might cause polyuria.

The third period is based on experimental physiology, and finds its origin in the work of Camus and Roussy,[28] who showed that injury to the floor of the third ventricle near the insertion of the infundibulum leads to polyuria, although Aschner [29] claimed priority in these experiments. The work of Camus and Roussy has been repeatedly confirmed, by Houssay and Hug,[30] Bailey and Bremer,[31] Hanchett,[32] Curtis [33] and others.

Leschke [21] was among the first to maintain that diabetes insipidus is due to a lesion at the base of the midbrain, and he based his arguments on a large amount of clinical material. He gave protocols of sixteen cases in which there was complete destruction of the hypophysis without polyuria. A careful study of such cases was made by Hann,[34] who compared them with cases of diabetes insipidus in which disease of the hypophysis was found. He concluded that the occurrence of polyuria depends not only on the condition of the posterior lobe, but on that of the anterior lobe as well. Disturbances of the posterior lobe with an intact anterior lobe lead to diabetes insipidus. If the anterior lobe is injured at the same time as the posterior lobe, diabetes insipidus does not develop. Extension of the process to the anterior lobe may cause an existing diabetes insipidus to disappear. This would account for such cases as Simmonds [35] reported, in which metastasis from a carcinoma of the breast produced polyuria which later disappeared. That lesions of the base of the midbrain do not invariably produce polyuria, is abundantly proved by reports of cases, usually of tumors of the hypophyseal anlage, which involve this region and which are not associated with polyuria. I [36] recently recorded a case of internal hydrocephalus in which the tuber cinereum was reduced to the thinness of paper, and yet there was not any clinical evidence of diabetes insipidus.

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27. Spanbock and Steinhaus: Deutsche med. Wchnschr. **24**:828, 1898.

28. Camus, J., and Roussy, G.: Presse méd. **22**:517, 1914; Endocrinology **4**: 507, 1920.

29. Aschner, B.: München. med. Wchnschr. **1**:81, 1917.

30. Houssay, B. A., and Hug, E.: Rev. Asoc. méd. argent. **34**:56, 1921.

31. Bailey, Percival, and Bremer, Frederic: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.

32. Hanchett, M.: Proc. Inst. Med., Chicago **3**:202, 1921.

33. Curtis, G. M.: Production of Experimental Diabetes Insipidus, Arch. Int. Med. **34**:801 (Dec.) 1924.

34. Von Hann, F.: Frankfurt. Ztschr. f. Path. **21**:337, 1918.

35. Simmonds: Verhandl. d. deutsch. path. Gesellsch. **17**:208, 1914.

36. Fink, E. B.: Internal Hydrocephalus and Hypopituitarism, Arch. Neurol. & Psychiat. **17**:332 (March) 1927.

As a result of the implication of the base of the brain in the genesis of diabetes insipidus, numerous histologic studies of this region have been made. An excellent summary of the anatomy and pathology of the vegetative centers of the midbrain was given by Greving.[37] Collections of ganglion cells and fiber tracts have been found in the tuber cinereum, corpus mammillare and adjacent tissue. That the centers in the tuber cinereum exert a regulatory influence on water and salt

Fig. 1.—A section of the hypophysis from a recent case of diabetes insipidus, showing the largest amount of glandular tissue found in the specimen. Low magnification.

Fig. 2.—A section of the hypophysis from a recent case of diabetes insipidus showing the smallest amount of glandular tissue, fading out into scar tissue. Low magnification.

metabolism has undoubtedly been proved by experimental physiologists. That these centers act independently of the hypophysis has certainly not been demonstrated. Evidence is constantly accumulating that the hypophysis and the diencephalic centers form an anatomic and probably also a functional unit.

37. Greving, R.: Ergebn. d. Anat. u. Entwcklngsgesch. **24**:348, 1923.

Cajal [38] described nerve fibers passing into the neurohypophysis. Hoenig [39] found nerve fibers in the neurohypophysis and stalk as well as fibers passing through the infundibulum and apparently ending in the epithelial cells of the anterior lobe. Loewy [40] destroyed the posterior lobe of the hypophysis experimentally in animals, and after from ten to fourteen days examined the tuber cinereum in serial sections. He found degeneration of the nucleus para-opticus (Gudden) and injured cells in the tuber cinereum (ganglion parahypophysios). The cells of these nuclei send out fibers which pass through the infundibulum to the

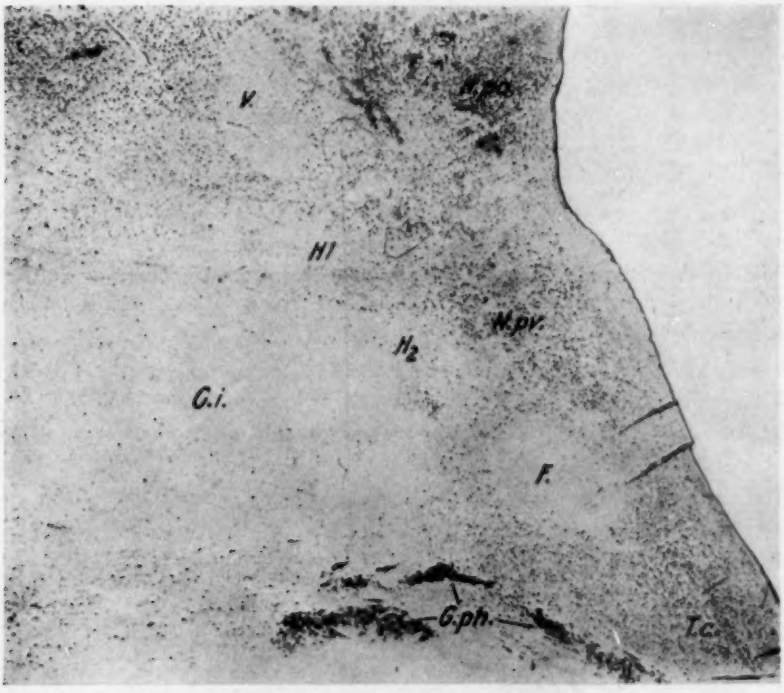

Fig. 3.—Frontal section through the hypothalamus and tuber cinereum of a human being. *C. i.* indicates internal capsule; *F,* fornix; *G. ph.,* ganglion parahypophysios; *H1, H2,* Forel's bundle; *N. pv.,* nucleus paraventricularis; *T. c.,* tuber cinereum. The ganglion parahypophysios extends from the region above the chiasm to the tuber cinereum (Clara Kary).

posterior lobe thus forming a united system, injury to any portion of which causes diabetes insipidus. Similar results were obtained by Clara Kary [41] who found axis cylinder fibers and only few glia cells in the infundibulum. Injury to the infundibulum led to degenerative changes in the tuber cinereum.

38. Cajal, Ramón y: Histologie du systeme nerveuz, Paris, 1911.
39. Hoenig, C.: Ztschr. f. d. ges. Neurol. u. Psychiat. **79**:197, 1922.
40. Loewy, F. H.: Deutsche med. Wchnschr. **48**:1663, 1922.
41. Kary, Clara: Virchows Arch. f. path. Anat. **252**:734, 1924.

TABLE 1.—*Observations at Necropsy in Cases of Diabetes Insipidus During Period Before Attention Was Centered on the Hypophysis, Showing Wide Diversity in Location of Lesions and Absence of Microscopic Studies*

Author	Reference	Pathology
Mosler.....	Virchows Arch. f. path. Anat. **43**: 225, 1868	Tumor of cavity of fourth ventricle the size of a walnut; description of hypophysis not given
Genilihomme...	Cited by Lancereaux: These de Paris, 1869, p. 17	No tumor or other gross change in brain; there was an exostosis of skull and gummas in liver
Massot.....	Lyon méd., 1872.....	Carcinoma of pineal body
Mosler.....	Virchows Arch. f. path. Anat. **57**: 51, 1873	Narrowing, thinning and softening of left half of medulla oblongata; in addition, isolated areas of softening in posterior half of left cerebral hemisphere; probably syphilitic
Dickinson.....	Diseases of the Kidney and Urinary Derangement, London, 1875	Tuberculous granulations of midbrain and internal hydrocephalus
Facio.....	Morgagni, September, 1879....	Sarcoma (?) the size of a chestnut at base of midbrain between chiasm and pons; most of chiasm was contained within tumor; hypophysis normal
Dreschfeld.....	Ztschr. f. Augenh., 1880, p. 108	Carcinoma of right base of midbrain resting on dura, extending anteriorly from right foramen opticum to clinoid process; hypophysis intact macroscopically
Moore.....	Brit. M. J., 1881, p. 108.....	Tumor of optic chiasm
Hagenbach....	Jahrb. f. Kinderh. **19**: 214, 1883	Tuberculous meningitis with dilatation of lateral and fourth ventricles; caseous tubercle in infundibulum, remainder of pituitary body not showing any change
Buttersack.....	Arch. f. Psychiat. **3**: 2, 1884	Syphilitic leptomeningitis of base of brain and spinal cord
Von Hoesslin..	Arch. f. klin. Med. **37**: 500, 1885	Hemorrhagic sarcoma (?) of pineal gland the size of a walnut, with extension to corpora quadrigemina; slight sclerosis of floor of fourth ventricle
Rath.....	Arch. f. Ophth. **34**: 81, 1888..	Spindle cell sarcoma (?) of hypophysis; intracellar portion the size of a small cherry; destruction of sella; main mass of tumor lies outside sella and extends into third ventricle; hypophysis transformed into tumor; no microscopic description
Weiszbarth....	Lancet **1**: 737, 1888.....	Edema of base of brain
Ganderer.....	Inaug. Diss., Giessen, 1889....	Teratoma of pineal body
Angelini.....	Società Lancisiana di Roma, December, 1889	Sarcoma of base of skull in anterior temporal fossa, with atrophy of optic and olfactory nerves and hemorrhagic softening in optic thalamus
Oppenheim.....	Spez. Path. u. Therap., vol. 9, pp. 52 and 77	Gumma lying between optic chiasm and base of midbrain; microscopically, pons and medulla entirely free
Oppenheim.....	Ibid.	Typical gummatous infiltration of optic chiasm, with infiltration of its central portion
Gerhardt.....	Ibid., vol. 7, part 1.....	Area of softening between left optic thalamus and lenticular nucleus and another at base of pons
Lepine.....	Handb. d. Harn. u. Sexual-Organe, section 4	Large tumor of optic thalamus
Chassaignac...	Quoted by Schümann: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **21**: 904, 1910	Skull fracture; contusion of frontal lobe
Jacquemont...	Ibid.	Skull fracture by blow on occiput
Friedberg.....	Ibid.	Depressed fracture of right parietal bone; red area of softening in cerebellum; fourth ventricle and its walls were intact
Stoermer.....	Ibid.	Severe commotio cerebri in railroad worker; death three years later; pons and medulla intact
Königshofer and Weil	Ophth. Klin., 1898, no. 10, p. 100	Meningeal sarcoma of base of brain extending from left foramen opticum behind chiasm destroying chiasm; hypophysis normal
Marinesco.....	Arch. orient. de méd. et de chir. **2**: 57, 1900	Gliosarcoma in floor of fourth ventricle
Edgren.....	Cited by Seigneurin: Thèse de Lyon, 1903-1904	Destruction of lower portion of lenticular nucleus and anterior portion of internal capsule, probably on syphilitic basis
Perroud.....	Ibid.	Syphilitic meningitis; cerebral softening; five gummas in brain
Pappenheimer.	Virchows Arch. f. path. Anat. **200**: 122, 1910	Tumor of pineal body
Baudouin and Mornas	Paris méd. **63**: 262, 1927.....	Cystic glioma in cerebellum

TABLE 2.—*Observations at Necropsy in Cases of Diabetes Insipidus Showing Involvement of the Hypophysis*

Author	Reference	Pathology
Rosenhaupt....	Berl. klin. Wchnschr., 1903 p. 153	Sarcoma (?) of thyroid with metastases to hypophysis
Zak.....	Wein. klin. Rundschau, 1904, p. 165	Tumor of hypophysis joined to base of brain
Erdheim and Goetzel	Ztschr. f. Heilk., 1905, p. 38..	Tumor of base of brain extending into third and lateral ventricles; internal hydrocephalus; atrophy of cells of anterior lobe; extensive lymphocytic infiltration in posterior lobe and capsule
Hunin.....	Cited by Lucien and Parisot: Rev. neurol. **17**: 976, 1909	Thick caseous tubercle in infundibulum
Borelli.....	Gior. d. r. Accad. di med. di Torino **76**: 91, 1913; abstr., Brit. M. J., 1913, epitome 65	Mass of caseating tissue occupying middle cranial fossa and sella turcica; entire pars nervosa, entire pars intermedia and about one fifth of pars anterior was invaded; no lesion within brain is mentioned
Berblinger.....	Verhandl. d. Deutsch. path. Gesellsch. **16**: 273, 1913; discussion, Ibid. 1914, vol. 17	Sarcoma of both frontal lobes extending into stalk and posterior lobe of pituitary body
Goldzieher.....	Ibid. **16**: 281, 1913.....	Compression of pituitary body by gumma resting on sella turcica; stalk and posterior lobe had completely disappeared, their place being occupied by tough scar tissue; pars intermedia and anterior lobe did not show distinct histologic change
Goldzieher.....	Ibid.	Hypophysis macroscopically apparently normal; microscopically, cystic adenomatous degeneration of pars intermedia extending to pars nervosa with fibrosis of pars nervosa
Simmonds.....	München med. Wchnschr. **60**: 127, 1913; ibid. **61**: 180, 1914	Recurrent carcinoma of breast; pars nervosa completely destroyed by metastatic nodule; remainder of pituitary body and stalk not invaded; no lesion found in brain
Simmonds.....	Ibid.	Recurrent carcinoma of breast with metastases; pars nervosa completely destroyed; remainder of gland and stalk not invaded; no lesion found in brain
Simmonds.....	Ibid.	Recurrent carcinoma of breast; carcinoma metastasis the size of a pea which has destroyed neurohypophysis, pars intermedia, stalk and anterior part of pars anterior
Cushing.....	Boston M. & S. J. **168**: 901, 1913	Recurrent lymphosarcoma of neck with metastases; discrete nodule of lymphosarcoma occupying stalk
Cushing.....	Ibid.	Interpeduncular tumor of pituitary duct; hypophysis greatly flattened and contained but a few normal elements
Von Gierke.....	Verhandl. d. deutsch. path. Gesellsch. **17**: 200, 1914	Carcinoma metastasis in pineal gland; hypophysis apparently normal macroscopically; microscopically, posterior lobe and infundibulum, cellular and contained a number of tubercles
Schmorl.....	Discussion, Verhandl. d. deutsch. path. Gesellsch. **17**: 208, 1914	Three cases of carcinoma metastases in posterior lobe; one case of primary tumor of pituitary stalk
Fraenkel.....	Ibid.	Two cases: metastatic carcinoma of breast in posterior lobe; primary tumor of pituitary stalk
Meyenberg.....	Beitr. z. path. Anat. u. allg. Pathol. **61**: 550, 1915	Destruction of greater part of pars nervosa and pars intermedia by tuberculosis, pars anterior being much less affected; no lesion found in brain
Meyenberg.....	Ibid.	Whole of gland with exception of small part of pars anterior replaced by malignant epithelial tumor; no lesion found in brain
Sequeira.....	Brit. J. Dermat. **27**: 186, 1915	Two cases of gumma of posterior lobe
Weber and Schmidt	Am. J. M. Sc. **152**: 892, 1916	Posterior portion of pituitary body was considerably enlarged and almost completely surrounded anterior portion; it was composed chiefly of large granular cells; anterior lobe was normal in structure; no lesion of brain
Sekiguchi.....	Ann. Surg. **63**: 297, 1916.....	Recurrent carcinoma of breast with metastases; pars posterior completely replaced by metastasis; no pathologic changes in gray matter of third ventricle

TABLE 2.—*Observations at Necropsy in Cases of Diabetes Insipidus Showing Involvement of the Hypophysis—Continued*

Author	Reference	Pathology
Sekiguchi.....	Ibid.	Recurrent carcinoma of breast with metastases; in capsule and one part of pars posterior near pars intermedia, there was a metastatic mass; no changes in third ventricle
Berge and Schulmann	Presse méd. **26**: 618, 1918....	Gumma of posterior lobe
Luzzatto.....	Sperimentale **71**: 405, 1918....	Destructive hemorrhage of posterior lobe, separating latter from infundibulum
Spanbock.....	Cited by Maranon.....	Gumma of posterior lobe
Neubürger.....	Berl. klin. Wchnschr. **57**: 10, 1920	Posterior lobe, pars intermedia and stalk completely infiltrated by secondary mammary carcinoma
Chauffard.....	M. Press & Circ. **110**: 142, 1920	Fungus tumor destroying hypophysis without involving basal tissue
Verron.....	Centralbl. f. allg. Pathol. u. path Anat. **31**: 521, 1921	Case 5: tumor of anterior lobe of hypophysis lying between anterior lobe and pars intermedia, confined within sella and invading particularly pars intermedia and stalk
Verron	Ibid.	Case 6: primary carcinoma of bronchi with metastases to posterior lobe and infundibulum
Reverchon and Worms	Bull. et mém. Soc. de chir. de Paris, 1921	Basal skull fracture; pituitary body reduced to mere nodule surrounded by dense capsule of fibrous tissue
Nonne.....	Deutsche Ztschr. f. Nervenh. **74**: 1, 1922	Calcified gumma involving entire hypophysis with exception of part of anterior lobe
Camus, Roussy and LeGrand	Compt. rend. Soc. de biol. **86**: 719, 1922	Abscess the size of a walnut which entirely destroyed pituitary; macroscopically there was no apparent lesion of infundibulum; microscopically, interstitial cellular infiltration of optopeduncular region
Jungmann.....	Deutsche med. Wchnschr. **48**: 1628, 1922; Klin. Wchnschr. **2**: 18, 1923	Ruptured appendix, general peritonitis; abscess of hypophysis surrounded by connective tissue; microscopically, abscess had destroyed greater part of anterior lobe and markedly compressed and injured posterior lobe
Pincherle and Magin	Arch. di pat. e clin. med. **3**: 261, 1924	Signs of active inflammatory reactions and advanced sclerosis of hypophysis with moderate neuroglia proliferation and slight degenerative lesions of tuber cinereum
Piney and Coates	J. Path. & Bact. **27**: 211, 1924	Recurrent carcinoma of breast with metastases to many parts of cerebrum and cerebellum; somewhat necrotic metastases in left optic thalamus; posterior lobe completely replaced by masses of carcinoma cells; no invasion of infundibulum or floor of third ventricle
Domagk.....	Klin. Wchnschr. **2**: 124, 1923..	Carcinoma of stomach: macroscopically, hypophysis was apparently normal; microscopically, posterior lobe was almost completely replaced by metastasis
Cox and Sloan	J. A. M. A. **82**: 2021, 1924....	Melanosarcoma metastasis in posterior lobe of hypophysis and infundibulum; base of brain not grossly infiltrated
Fink.....	Endocrinology **10**: 317, 1926..	Infundibulum, posterior lobe and pars intermedia replaced by dense scar tissue; only a remnant of anterior lobe was left; no changes in tuber cinereum

The relationship between the hypophysis and diencephalic centers was studied extensively by Espino [42] who found that comparative anatomy furnishes evidence of a close relationship between the hypophysis and diencephalon in the entire series of animals possessing an hypophysis. In man such a relationship exists between the tuber

42. Espino, A. V.: Contribución al Estudio de las Relationes entra la hypófisis y los Centros Diancephalicos, Thesis, University of Mexico, 1924.

TABLE 3.—*Observations at Necropsy in Cases Reported as Not Being Due to a Lesion of the Pituitary Body*

Author	Reference	Pathology
Facio.....	Morgagni, September, 1879...	Sarcoma (?) the size of a chestnut at base of midbrain between chiasm and pons; most of chiasm was contained within tumor; hypophysis normal
Königshofer and Weil	Ophth. Klin., 1898, no. 10, p. 100, 1898	Meningeal sarcoma of base of brain extending from left foramen opticum behind chiasm destroying chiasm; hypophysis normal
Meyer.....	Deutsches Arch. f. klin. Med. **83**: 1, 1905; Berl. klin. Wchnschr. **44**: 1642, 1912	Encephalitis of corpora mammillaria; infundibulum and hypophysis intact
Bartels.....	Ztschr. f. Augenh. **16**: 8, 1906	Squamous cell carcinoma of base of brain, the size of a hen's egg, extending into third ventricle; destruction of stalk; hypophysis, normal in size and histology, lay in sella
Finkelnberg....	Arch. f. klin. Med. **91**: 345, 1907; Sitzungsb. d. niederhein. Ges. f. Natur. u. Heilk., 1910, p. 45	Cystic hypophyseal duct tumor between floor of third ventricle and normal hypophysis, which was somewhat flattened
Haushalter and Lucien	Rev. neurol. **16**: 79, 1908.....	Tumor the size of a hazelnut at base of brain, at border of tuber cinereum, pushing floor of midbrain upward; infundibulum not altered; microscopically hypophysis well preserved
Knobloch and Fischer	Klinik und Atlas der Chronischen Krankheiten des Zentralnervensystems, Berlin, Julius Springer, 1909	Glioma of roof of third ventricle; hypophysis intact and showed only slight hyperemia and hyperplasia as well as increased pigment in posterior lobe; interpeduncular region and corpora mammillaria not involved
Standhartner..	Cited by Lucien and Parisot: Rev. neurol. **17**: 976, 1909	Tumor at base of midbrain
Cushing.....	Boston M. & S. J. **168**: 901, 1913	Interpeduncular cystic tumor; hypophysis was greatly flattened and contained but few normal cellular elements
Simmonds.....	München. med. Wchnschr. **60**: 127, 1913; **61**: 180, 1914	Sarcoma the size of a walnut in region of third ventricle extending into stalk and pars nervosa
Harris and Graham	Lancet **2**: 1251, 1913.....	Tumor the size of a peach on floor of third ventricle above infundibulum, compressing tracti optici; hypophysis somewhat compressed but otherwise normal
Van den Bergh and Van Hasselt	Nederl. Tijdschr. v. Geneesk. **57**: 1271, 1913	Teratoma of pineal gland; metastasis occupying infundibulum; gland itself somewhat flattened but did not show histologic changes
Fleckseder.....	Wien. klin. Wchnschr. **28**: 867, 1914	Metastatic melanosarcoma replacing pars nervosa and stalk, growing through tuber cinereum and midbrain to third ventricle
Römer.....	Deutsche med. Wchnschr. **40**: 108, 1914	Tumor of base of brain invading stalk and posterior lobe of pituitary body; no adequate account is given of observations at necropsy
Nonne.....	Syphilis und Nervensystem, 1915; Deutsche Ztschr. f. Nervenh. **35**: 1, 1916	Calcified teratoma of hypophysis, greater part lying above sella and compressing midbrain
Nonne.....	Ibid.	Cell poor glioma at base of pons involving base of midbrain and compressing infundibulum; hypophysis itself intact
Nonne.....	Ibid.	Glioma between pons and base of midbrain which extended to corpora mammillaria and infundibulum; hydrocephalus of third ventricle; hypophysis normal macroscopically and microscopically
Claude and Lhermitte	Presse méd. **25**: 417, 1917....	Epithelial cystic tumor formed from wall of third ventricle and confined to infundibulum; hypophysis was entirely normal
Newmark.....	Arch. Int. Med. **19**: 550, 1917	Tumor of uncertain nature lying between cerebral hemispheres and occupying and distending entire third ventricle without invading brain substance; pars nervosa and greater part of pars intermedia had been destroyed by it
Fodor and Jankovitch	Orvosi hetil.; abstr., Neurol. Centralbl. **39**: 703, 1920	Tuberculous basilar meningitis; nodule the size of a hazelnut in floor of third ventricle; infundibulum almost as thick as hypophysis itself and consists of tuberculous tissue; hypophysis almost completely tuberculous; normal tissue present only in lower one third of anterior lobe
Riealdinf.....	Bull. et mém. Soc. méd. d. hóp. de Paris **44**: 769, 1920	Sarcoma between optic thalamus and tuber cinereum

TABLE 3.—*Observations at Necropsy in Cases Reported as Not Being Due to a Lesion of the Pituitary Body—Continued*

Author	Reference	Pathology
Maranon.....	Endocrinology **5**: 159, 1921...	Gunshot of head; shot lodged in parahypophyseal region; histologic examination of hypophysis showed that section of stem caused cicatrization which invaded posterior lobe
Verron.....	Centralbl. f. allg. Pathol. u. path. Anat. **31**: 521, 1921	Trauma; circumscribed necrosis of infundibulum
Nakamuro.....	Juzankwai Zasshi, 1922, vol. 27, no. 4; abstr., Japan M. World **2**: 266, 1922	Hemorrhage and inflammatory condition about base of cerebrum
Globus and Strauss	Arch. Neurol. & Psychiat. **8**: 53, 1922	Teratoid cyst of base of brain; both lobes and infundibulum were compressed
Lhermitte.....	Ann. de méd. **11**: 89, 1922....	Syphilitic lesion involving both infundibulum and tuber cinereum
Hamilton.....	Canad. M. A. J. **12**: 209, 1922	Tumor of circle of Willis
Martin and Cushing	Arch. Ophth. **52**: 209, 1923...	Glioma of optic chiasm compressing pituitary stalk and growing into region of third ventricle
Reverchon, Delater and Worms	Rev. neurol. **30**: 217, 1923....	Cystic tumor in region of infundibulum originating in sella turcica; infundibulum and region anterior to peduncles involved
Schükry.....	Ztschr. f. d. ges. Neurol. u. Psychiat. **86**: 488, 1923	Cystic tumor in region of infundibulum and third ventricle; hypophysis compressed
Pincherle and Magin	Arch. di pat. e clin. med. **3**: 261, 1924	Epidemic encephalitis; extensive and severe degenerative changes in ganglionic cells of tuber cinereum accompanied by intense phenomena of neuronophagia and perivascular infiltration; no histologic alteration in hypophysis
Meyer and Meyer-Bisch	Klin. Wchnschr. **3**: 1796, 1924	Sarcoma of base of skull; complete destruction of infundibulum and posterior lobe of hypophysis; only anterior lobe was partly preserved; tumor tissue had invaded midbrain but did not quite reach third ventricle
Horrax and Bailey	Arch. Neurol. & Psychiat. **13**: 423, 1925	Case 8: pinealoma and glioma of optic chiasm; hypophysis normal
Horrax and Bailey	Ibid.	Case 9: small pinealoma and large vascular glioma of third ventricle; hypophysis normal
Horrax and Bailey	Ibid.	Case 10: pinealoma; hydrocephalus internus
Josephy.....	Ztschr. f. d. ges. Neurol. u. Psychiat. **93**: 62, 1924	Neuroma and cyst of base of brain lying between optic tracts and cerebral peduncles; infundibulum could not be identified; hypophysis flattened
Kiyono.....	Virchows Arch. f. path. Anat. **257**: 477, 1925	Hypophysis flattened; atrophy of posterior lobe; round cell infiltration of infundibulum and centers in tuber cinereum
Thompson, Keegan and Dunn	Arch. Int. Med. **36**: 650, 1925	Fibrosis of tuber cinereum; slight subacute inflammation of pars posterior of pituitary gland
Babonniex and Lhermitte	Compt. rend. Soc. de biol. **93**: 1415, 1925	Syphilitic basilar meningitis and lesions in infundibulum and tuber cinereum; hypophysis was apparently normal

cinereum, infundibulum and hypophysis from early intra-uterine life. Embryologic studies indicate a diencephalic entity. Histologic examination of the centers in the tuber cinereum shows the cells to be distinctly ganglionic with nonmedullated efferent fibers which go through the infundibulum and pituitary stem. In all these facts there is nothing to indicate that the hypophysis does not bear any relation to the vegetative functions of the centers in the midbrain, and much in favor of its direct endocrine and indirect endocrine-vegetative influence.

I have been able to collect from the literature records of 107 necropsies in cases of diabetes insipidus. These are included in tables 1 to 3.

An analysis of the cases shows that sixty-eight patients, or 63 per cent, had tumors about the base of the brain or posterior cranial fossa. Fourteen, or 13 per cent, were due to syphilitic processes, either basal meningitis or gummas in or near the hypophysis. In five cases the lesion was a tuberculoma or tuberculous meningitis of the base, while nine were due to nonsyphilitic inflammatory conditions in the same location. The remainder are included under traumatic injuries.

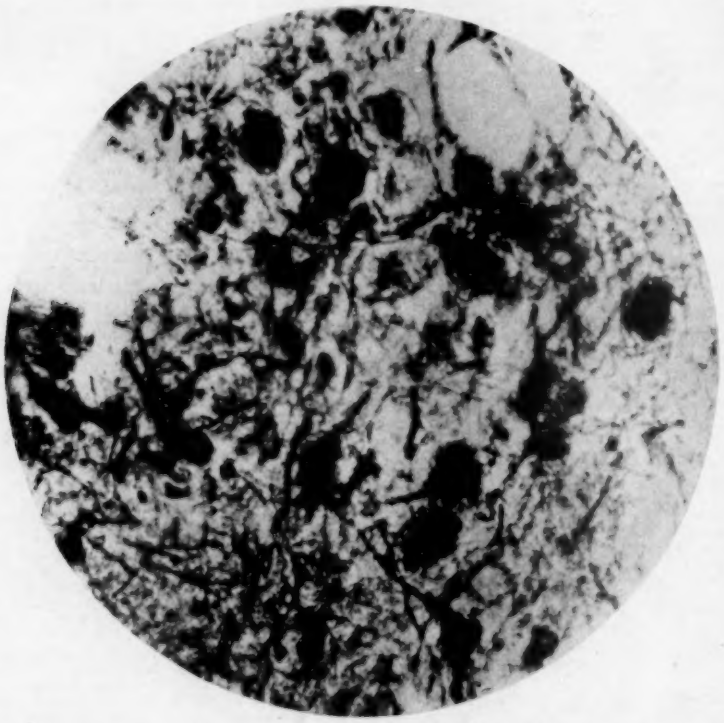

Fig. 4.—Cells of the nucleus hypophyseus (N. supra-opticus). Photomicrograph; × 295. (Pines: Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:123, 1925.)

The majority of the cases in which there was a tumor are not of localizing value, since they have involved more than one structure in the narrow space at the base of the brain. There are fifteen instances of a discrete metastatic carcinoma nodule limited to the posterior lobe of the hypophysis or infundibulum. Ten cases are on record of a gumma or caseous tubercle in the same situation. In a case belonging to the latter group recently reported by me,[43] a careful histologic study of the tuber cinereum failed to show any pathologic changes.

43. Fink, E. B.: A Case of Diabetes Insipidus Associated with Syphilis of the Hypophysis, Endocrinology **10**:317 (May-June) 1926.

DIAGNOSIS

The diagnosis of a typical case of diabetes insipidus does not offer any great difficulty. In the determination of the underlying pathology, syphilis, neoplasm, trauma or tuberculosis must be considered. A history of the removal of a malignant growth, usually of the breast, with the subsequent development of polyuria is an almost pathognomonic sign of a metastasis in the posterior lobe of the hypophysis. Rowntree [4] mentioned the following conditions to be considered for differential diagnosis:

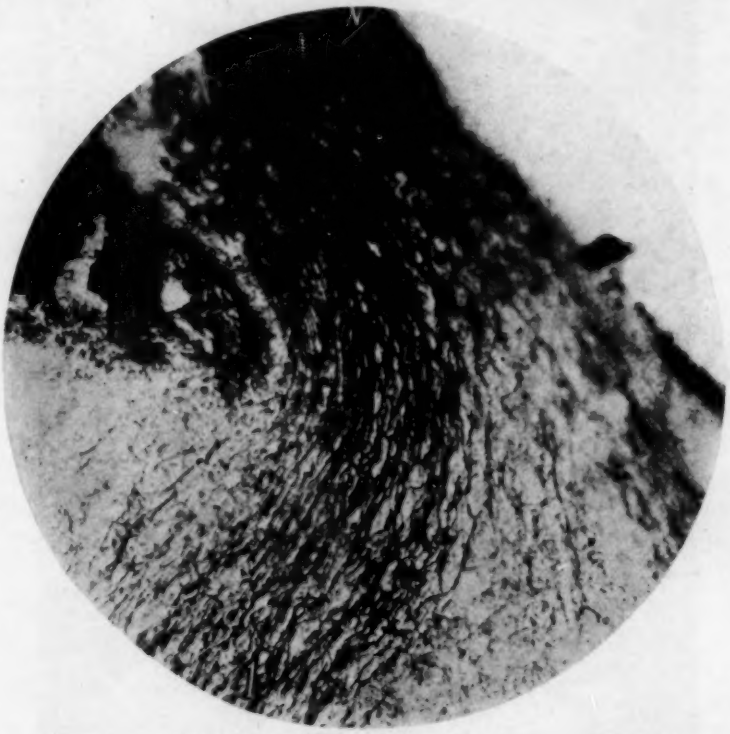

Fig. 5.—Nerve fibers arising in the center shown in figure 4, forming a compact bundle, bend mediodorsalward and pass toward the infundibulum, parallel to the wall of the third ventricle. Photomicrograph; × 175. (Pines.)

physiologic polyuria, diabetes mellitus, chronic diffuse nephritis, polycystic disease of the kidneys, acute infection of the kidney or of the urinary tract and functional disorders of the nervous system.

TREATMENT

Traumatic polyuria may terminate in spontaneous cure. When there is a syphilitic basis, antisyphilitic treatment gives variable results.

Usually permanent benefit does not result. In 1909, Ebstein [44] collected twenty-three cases of diabetes insipidus with syphilitic meningitis, in which the result of antisyphilitic treatment was known. Seventeen of the patients were benefited by antisyphilitic treatment; six were not benefited. Benario [45] reported seven cases in which either cure or improvement occurred under arsphenamine therapy. Umber [46] described a patient in whom the Wassermann reaction was positive in the blood

Fig. 6.—Fasiculus hypophyseus. A bundle of nerve fibers passing through the infundibulum to the posterior lobe of the hypophysis. This mass of fibers is a continuation of those shown in figure 5; × 335. *I* indicates infundibulum; *H*, posterior lobe of the hypophysis; *N*, nerve fibers; *D*, glandular anterior lobe. (Pines.)

and negative in the spinal fluid in whom syphilitic treatment resulted in complete recovery. Spinal puncture, first advocated by Herrick,[47] has

44. Ebstein, W.: Deutsches Arch. f. klin. Med. **95**:1, 1909.

45. Benario: München. med. Wchnschr. **60**:1768, 1913.

46. Umber: Deutsche med. Wchnschr. **48**:1221, 1922.

47. Herrick, J. B.: Report of a Case of Diabetes Insipidus with Marked Reduction in the Amount of Urine Following Lumbar Puncture, Arch. Int. Med. **10**:1 (July) 1912.

proved of little real value. The restriction of water accomplishes nothing, is an unnecessary cruelty and may even be dangerous.

In the experience of Allen and Sherrill,[19] restriction of protein and salt caused a reduction in thirst and polyuria, whereas heavy protein feeding caused an increase in these symptoms with a flushing out of the chlorides. The restriction of sodium chloride is more essential than the restriction of nitrogen. The best results were obtained when sodium chloride was restricted to the extent that less than 1 Gm. appeared in the twenty-four hour specimen of urine, and this was not followed by any untoward effect.

The most important contribution to the treatment of diabetes insipidus was made by von den Velden [48] in 1913, when he demonstrated that in persons with normal kidneys the subcutaneous injection of pituitary extract produces a reduction in diuresis instead of an increase, as had been previously indicated by physiologic experiments (Magnus and Schäfer,[49] Schäfer and Herring [50]). In addition, there is a more or less marked retention of water and sodium chloride. Definite inhibition begins from two to four hours after the injection and lasts until the second day. An injection of 1 cc. possesses this action. The therapeutic effect of pituitary is so striking that Hoppe-Seyler [51] believed that the only thing necessary to restore normal conditions in patients with diabetes insipidus is a trace of pituitary extract. The observations of von den Velden have been repeatedly confirmed. The action of pituitary extract on the tissues is probably pharmacologic, and is not a replacement therapy. The greatest objection to the use of pituitary extract is the need for repeated hypodermic injections. This may be overcome in cases in which it is effective, by nasal application, by means of a spray, a medicine dropper or a tampon, as suggested by Blumgart.[52]

SUMMARY AND CONCLUSIONS

Diabetes insipidus is a clinical syndrome without a uniform pathologic basis. A study of necropsy reports shows that there are cases on record which can be used in favor of any theory one may wish to favor.

Experimental polyuria has been produced by lesions in the floor of the fourth ventricle, separation of the pituitary stalk, injury or stimulation of the tuber cinereum, corpora quadrigemina, pons and cerebellum. Every part of the base of the brain has been implicated at one time or another.

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48. Von den Velden, R.: Berl. klin. Wchnschr. **50**:2083, 1913.
49. Magnus and Schäfer: J. Physiol. **9**:27, 1901.
50. Schäfer and Herring: Phil. Tr. Roy. Soc., London **199**:1, 1906.
51. Hoppe-Seyler: München. med. Wchnschr. **62**:1633, 1915.
52. Blumgart, H. L.: Antidiuretic Effect of Pituitary Extract Applied Intranasally in a Case of Diabetes Insipidus, Arch. Int. Med. **29**:508 (April) 1922.

In considering the pathology of diabetes insipidus, those cases in which the lesion is confined to the posterior lobe and infundibulum of the hypophysis cannot be ignored. When polyuria develops in a case of malignancy, it is almost a pathognomonic sign of a metastasis in the posterior lobe of the hypophysis.

The posterior lobe of the hypophysis is a part of the diencephalon, both genetically and anatomically. In the light of present knowledge, the hypophysis and the centers in the midbrain must be considered as a functionally united system. Injury of any part of this system may result in diabetes insipidus, although it does not invariably do so. The underlying factors that determine in a given case whether polyuria shall or shall not develop are not known.

The theory that harmonizes most closely with the facts is that the function of the kidney is under the influence of three factors: the kidney itself and its autonomic nerves; a vegetative center, probably located in the tuber cinereum, and a pituitary hormone. Injury to, failure of function of or irritation in, any of these controlling factors may result in the symptom-complex diabetes insipidus.

Notes and News

University News, Promotions, Resignations and Appointments.—Ernest M. Hall of the department of pathology in the Stanford School of Medicine has assumed the position of pathologist at St. Vincent's Hospital, Los Angeles.

J. J. R. MacLeod, professor of physiology in the University of Toronto, has accepted the regius professorship of physiology in the University of Aberdeen, Scotland.

Edmund V. Cowdry of the Rockefeller Institute for Medical Research has been appointed professor of cytology in Washington University Medical School, St. Louis.

J. C. Geiger, formerly assistant commissioner of health of Chicago, is now associate professor of epidemiology in the University of California Medical School.

Charles V. Chapin, for many years health officer of Providence, R. I., has been awarded a public welfare medal by the National Academy of Sciences for his work in public health.

At the University of Chicago, Sigfried Maurer has been promoted to assistant professor of pathology under the Sprague Institute, and Estace L. Benjamin has been appointed instructor in pathology.

Richard H. Jaffe, professor of pathology and bacteriology in the University of Illinois College of Medicine, has been appointed director of the pathologic laboratories of the Cook County Hospital, Chicago.

Two memorial volumes containing articles by Italian and foreign scientists have been published to commemorate the completion of thirty-five years of service as professor of general pathology in the University of Turin by Benedetto Morpurgo.

Reuben L. Kahn of the department of health of the state of Michigan has been appointed director of the laboratories of the hospital and assistant professor of clinical bacteriology and serology in the University of Michigan Medical School.

Ferdinand C. Helwig has been appointed full time pathologist to St. Luke's Hospital, Kansas City, Mo.

At the University of California Medical School, San Francisco, Glanville Y. Rusk has been promoted to professor of pathology.

Abraham Flexner has resigned as director of the division of studies and medical education of the General Education Board, New York.

Committee on Research in Syphilis.—It is the purpose of this committee to spend the funds placed at its disposal on a constructive program of research in syphilis. It plans to stimulate, through grants, researches which are already in progress or which are to be undertaken. Applications for grants should be addressed to Dr. John H. Stokes, 3800 Chestnut Street, Philadelphia. The headquarters of the committee is located at 370 Seventh Avenue, New York; Dr. Edward L. Keyes is chairman of the executive committee; Dr. John H. Stokes (Philadelphia) is chairman of the scientific committee, and D. W. J. M. A. Maloney is the secretary.

John J. Abel Fund for Research on the Common Cold.—The Chemical Foundation has given $195,000 to the school of hygiene and public health of Johns Hopkins University for the study of the origin, nature and possible cure of the common cold.

Death of Oskar Bail.—Oskar Bail, director of the Hygienic Institute of the German University in Prague, died after a prolonged illness. Bail was born in 1869 and began to work under Hueppe in Prague in 1897. He was perhaps known best as the author of the aggressin hypothesis, but his recent work on the bacteriophage also attracted much attention.

Death of Karl K. Koessler.—Karl K. Koessler, professor of pathology under the Sprague Institute in the University of Chicago, and associate clinical professor in the department of medicine of Rush Medical College, died Feb. 17, 1928.

Society News.—The Society for Experimental Biology and Medicine has elected Stanley R. Benedict president, Peyton Rous, vice president, and A. J. Goldforb, secretary.

At the last annual meeting of the Chicago Pathological Society, Esmund R. Long was elected president, Henry C. Sweany vice president, Edwin F. Hirsch, secretary, and A. A. Goldsmith, treasurer.

At the annual meeting of the American Society for Experimental Pathology, held in Ann Arbor, April 12, 13 and 14, 1928, the following officers were elected for the ensuing year: Edward B. Krumbhaar, president; William F. Petersen, vice president; Carl V. Weller, secretary-treasurer; Frederick L. Gates and Samuel R. Haythorn, councilors. The president and secretary of the Society for Experimental Pathology hold similar positions in the Federation of American Societies for Experimental Biology for 1928-1929. The next meeting of the Federation will be merged with that of the International Physiological Congress to be held in Boston in August, 1929. The scientific proceedings of the Ann Arbor meeting of the Society for Experimental Pathology are reported elsewhere in THE ARCHIVES.

Congress of Russian Pathologists.—The first union congress of Russian pathologists met in Kiev in September, 1927. More than 600 delegates from all parts of Russia participated in the congress. The subjects discussed were (1) tissue cultures and problems of pathology; (2) problems of malignant tumors; (3) the reticulo-endothelial system. It is proposed to hold the second congress in 1929 in Baku in the Caucases.

Pathologic Commission of Kiev Academy of Science.—This academy has a pathologic-anatomic commission of which N. F. Melnikov-Rasvedenkov is president, which has organized a museum of ethnographic and geographic pathology. The commission also collects and studies the brains of noted scientists.

Biographical Directory of American Men of Science.—The fourth edition of the Biographical Directory of American Men of Science has been published by the Science Press, Grand Central Terminal, New York. This book contains the records of about 13,500 living men of science.

Milbank Fund for International Study of Infantile Paralysis.—Jeremiah Milbank of New York has given $250,000 for a three year cooperative study of infantile paralysis here and abroad. William H. Park is the chairman of the committee in charge.

Abstracts from Current Literature

Pathologic Physiology

THE RESPIRATORY EXCHANGE OF DIABETIC AND NONDIABETIC DOGS FOLLOWING HEPATECTOMY. J. MARKOWITZ, Am. J. Physiol. **83**:698, 1928.

As a result of the study of the respiratory quotient in dogs hepatectomized by Mann's three-stage operation, in dogs with both liver and pancreas removed, in dogs surgically or functionally hepatectomized and eviscerated and in dogs functionally hepatectomized by an Eck fistula along with ligation of the hepatic artery, the writer concludes that there is no evidence of inability of a depancreatized animal to oxidize carbohydrate. So that the sugar which appears in the urine of depancreatized dogs is not the sole metabolic expression of all the dextrose produced in the animal's body, and calculations based on such elimination of sugar cannot safely be used as evidence that carbohydrate is not being formed from the fatty acids of the animal.

H. E. EGGERS.

THE INTERRELATIONSHIP OF THE CARRIERS OF VITAMINS A AND B AS AFFECTING THE GROWTH AND DEVELOPMENT OF THE TISSUES AND ORGANS OF YOUNG ANIMALS. J. E. RICHARDSON, L. S. PALMER and C. KENNEDY, Am. J. Physiol. **83**:712, 1928.

Rats fed with presumably adequate rations made up of highly purified food materials and including standard amounts of protein, salts and vitamins A and B, showed failure to grow at the normal rate, remained sexually immature, and often developed greasy skin and hair. These abnormalities were not the result of deficiency in vitamins A and B, and apparently were caused by faulty fat metabolism or utilization. It would seem that in the course of food purification some compound had been removed necessary for the proper utilization of fat. Some indications were found of important interrelations between the carriers of vitamins A and B.

H. E. EGGERS.

THE THYROID GLAND AND THE SENSITIVITY OF ANIMALS TO INSULIN. S. W. BRITTON and W. K. MYERS, Am. J. Physiol. **84**:132, 1928.

The reaction of selected, vigorous cats to insulin was studied before and after complete thyroidectomy. From ten to twenty days after the operation there was observed a definite increase in sensitivity to insulin, not referable to operative trauma, to the extent that about one half of the preoperative reactive dose of insulin was now sufficient to induce hypoglycemic symptoms. The animal completely recovered from this in from twenty to thirty days after operation. Within five or six weeks, there was a heightened tolerance to insulin. During the period of postoperative hypersusceptibility, the hypoglycemic manifestations could be effectively abolished by the administration of posterior pituitary extract. The thyroidectomy did not have an effect on the induction of typical epinephrine hyperglycemia. If the suprarenal medulla was removed in a thyroidectomized animal, there was marked and persistent hypersusceptibility to insulin. In this case, the injection of epinephrine during shock resulted in rapid recovery. In fasting thyroidectomized animals and in one animal in which both thyroid and suprarenal medulla had been removed and which was killed during hypoglycemic convulsions, the liver and muscle were found to contain normal amounts of glycogen. Apparently thyroidectomy and subsequent ablation of the suprarenal medulla, as well, does not affect glycogen storage. However, there appears to be reduced ability to mobilize carbohydrate reserves in these conditions—a temporary effect in the case of the thyroid and a more severe and permanent one in the case of the suprarenal.

H. E. EGGERS.

MEDULLIADRENAL SECRETION AND CARBOHYDRATE METABOLISM. S. W. BRITTON, E. M. K. GEILING and H. O. CALVERY, Am. J. Physiol. **84**:141, 1928.

The susceptibility of cats to insulin was determined before and after medullisuprarenal inactivation either by medullectomy or by removal of the right suprarenal gland and denervation of the left. Both showed the same symptoms—a striking increase in susceptibility, amounting to a four to tenfold increase. This hypersusceptibility was only slightly further increased by the administration of ergotamine tartrate. There was no increase in blood sugar of the animals following the hypoglycemic convulsions, and recovery took place only after the injection of dextrose or epinephrine. Spontaneous recovery was not unusual in animals with intact suprarenals. The effect of the injection of small amounts of epinephrine in medullectomized animals was a rapid elevation of blood sugar; correspondingly large changes were not observed in intact animals. The increased sensitivity persisted without notable change for more than four months. Complete protection in this condition was afforded by the administration of small does of epinephrine, begun shortly after the injection of insulin and repeated at suitable intervals. From the fact that in the animals which had been operated on a lowering of the glycogen content of the liver during the hypoglycemic conculsions did not occur, it is concluded that the depletion of the hepatic store of glycogen, to replace a deficiency of sugar in the blood, is largely dependent on a secretion from the suprarenal medulla. Lack of this secretion is not incompatible with life, but manifests itself in certain critical circumstances.

H. E. EGGERS.

THE PREPARATION OF A STERILE, ACTIVE EXTRACT FROM THE ANTERIOR LOBE OF THE HYPOPHYSIS. T. J. PUTNAM, H. M. TEEL and E. B. BENEDICT, Am. J. Physiol. **84**:157, 1928.

A method is described for the preparation of a sterile active extract of the anterior lobe of the hypophysis. The effect of this extract was to enhance the rate of growth of rats and dogs—in the latter, only after long and persistent injection—with the development of certain acromegaloid changes in the bones of the dog. In hypophysectomized dogs and rats, restoration of growth was observed, along with increased rate of growth of the hair and repair of the wound. Apparently it is as effective in arresting estrus in the rat as the emulsion of the gland itself. In one human case of pituitary insufficiency, it afforded apparent temporary benefit.

H. E. EGGERS.

OBSERVATIONS ON PARATHYROIDECTOMIZED DOGS, WITH PARTICULAR ATTENTION TO THE REGIONAL INCIDENCE OF TETANY, AND TO THE BLOOD MINERAL CHANGES. C. I. REED, R. W. LACKEY and J. I. PAYTE, Am. J. Physiol. **84**:176, 1928.

The following is a summary of the observations on thirty-five parathyroidectomized dogs: Laryngospasm was the commonest symptom in puppies; there was greater susceptibility to infection in these animals; during the presence of a complicating infection, only one animal showed tetanic manifestations; the operation did not have an effect on estrus and pregnancy; the tetany level of the calcium varied in different animals and at different times in the same animal; tetany practically always occurred when the ratio of calcium to phospherus was 1 or less; the product Ca×P did not bear any relation to the incidence of tetany; there was no relation between the severity of the tetany and the Ca : P ratio, or the absolute concentration of either element at the critical ratio; relations were not observed between barometric pressure and the occurrence of tetany; changes of mineral content of the blood did not explain all of the facts observed.

H. E. EGGERS.

THE INFLUENCE OF CEREBRAL BLOOD FLOW ON RESPIRATION: I, II AND III. C. F. SCHMIDT, Am. J. Physiol. **84**:202, 223 and 242, 1928.

A method is described for measuring the cerebral blood flow as arterial inflow and venous outflow, and for perfusing the brain with measurable amounts of blood, in spontaneously breathing cats and dogs. With this method, the following observations are reported: The cerebral blood flow varies with changes in systemic pressure, without direct vasomotor influences of sufficient strength to be revealed by the method used. There is, however, intrinsic chemical control of the cerebral vessels, as shown by dilatation by carbon dioxide, anoxemia, acid, heat and cerebral anemia; constriction occurs with excess oxygen, alkali and cold, and probably with increased blood flow. Respiratory depression follows increased blood flow, even during inhalation of carbon dioxide or nitrogen. Respiratory stimulation is caused, within certain limits, by decreased blood flow; beyond these limits a further reduction in flow depresses breathing and an increase then stimulates it. This condition, to which Schmidt applies the term "reversal," is due to insufficient oxygen supply to the brain; it can also be produced by decreased oxygen content in the blood, and by stimulation as by electrical means or carbon dioxide in the presence of diminished blood flow. The gaseous metabolism of the brains of the dogs varies widely with different animals, but tends to parallel respiratory activity. When the latter is altered, there is a corresponding change of cerebral metabolism, except in the case of inhalation of carbon dioxide. "Reversal" was found to coincide with a reduction of the ability of the brain to absorb oxygen from the blood, so that it is a toxic effect of lack of oxygen. Schmidt's general conclusions are as follows: The chief function of the entire respiratory mechanism is the maintenance within the center of a constant concentration of stimulant material. Known factors in this maintenance are changes in the arterial blood occurring in the lung, acid excretion by the kidneys, changes in the metabolic activity of the center itself and changes in the blood supply of the center. A primary change in the accumulated metabolites in the center leads, through the respiratory response, to compensatory changes in the blood. A primary change in external stimuli leads to compensatory changes in the internal stimuli, through changes in the blood vessels of the center and vasomotor response. The exact nature of the stimulant material cannot as yet be determined, but it is derived from cellular metabolism, and carbon dioxide appears to be of greater importance than lack of oxygen, in view of the "reversal" induced by the later.

H. É. EGGERS.

CIRCULATORY COLLAPSE IN DIPHTHERIA. C. W. EDMUNDS and F. D. JOHNSTON, J. A. M. A. **90**: 441, 1928.

For the present, the evidence is that the fatal circulatory collapse is due primarily to an action of the toxin on the receptive substance of the splanchnic nerves, producing a loss of control of the abdominal vessels by these nerves. The vessels relax and the blood pressure falls, resulting in a deficiency in the amount of blood returned to the heart. The general arterial pressure falls also, causing an anemia of the medullary centers and possibly death. There is therefore a distributive oligemia from the failure of the splanchnics and, in addition, profound myocardial changes. The importance of the latter in the functional activity of the heart it is impossible to estimate. AUTHORS' SUMMARY.

EFFECT OF SIXTY-THREE DAYS OF A PROTEIN-FREE DIET ON NITROGEN PARTITION PRODUCTS IN URINE AND ON HEAT PRODUCTION. H. J. DUEL, I. and K. SANDIFORD and W. BOOTHBY, J. Biol. Chem. **76**:391, 1928.

EFFECT OF THYROXIN ON RESPIRATORY AND NITROGEN METABOLISM OF A NORMAL PERSON FOLLOWING PROLONGED NITROGEN-FREE DIET. Ibid,, p. 407.

The minimum total quantity of nitrogen observed in the twenty-four hour urine from a normal man, during thirty days of maintenance on a nitrogen-free

diet, was 2.1 Gm. During a subsequent period of greater exhaustion of the protein reservoirs, following the administration of thyroxin, a second record minimum of 1.75 Gm., corresponding to 0.024 Gm. per kilogram of body weight, was obtained. Sixteen per cent of the original body weight was lost during the experiment. The basal metabolic rate decreased rapidly to a lower, constant level. The output of creatinine, uric acid, neutral sulphur and ethereal sulphate remained constant. The only fluctuation in elimination of nitrogen observed was in the amount of urea excreted.

The effect of administration of thyroxin on the nitrogenous and respiratory metabolism of a person whose protein reservoirs have been depleted as the result of maintenance for thirty days on a protein-free diet is substantially the same as its effect on a normal person.

(The diet used consisted mainly of sugar and cornstarch administered first as a pudding and later as an aqueous suspension. The authors state that physiologic disturbances were not incurred other than a slight nausea occasioned toward the end of the period by the monotony of the diet.)

ARTHUR LOCKE.

REACTIONS OF LYMPHATICS, WITH SPECIAL REFERENCE TO THOSE OF THE DIAPHRAGM. HOWARD FLOREY, Brit. J. Exper. Path. **8**:479, 1927.

The pleural surface of the diaphragm of animals is observed by quickly removing the thorax immediately after death. Bathed in Ringer-Locke solution at 37 C., the lymphatic trunks but not the lymphatic capillaries (of guinea-pigs only), are seen to contract rhythmically, and this contraction can be increased in rate by the application of epinephrine. A special preparation of graphite injected intraperitoneally is taken up by the peritoneal lymphatics of the diaphragm at a much increased rate when the intra-abdominal pressure is increased. These particles appear to pass through, and are found in, the spaces between the mesothelial cells, few of them being present in the cell protoplasm itself. An analogy is drawn between these phenomena and the absorption by lymphatics of fat and other particles in general.

S. D. SIMON.

PHYSIOLOGIC MODIFICATIONS IN A HUMAN ORGANISM DURING FLIGHT: METHODS OF EXAMINATION IN SELECTION OF AIR PILOTS. FRANCESCO F. LELLI, Arch. di anthrop. crim. **4**:762, 1927.

Physical and mental states of a human being in a condition to which he is unaccuctomed presents interesting physiologic variations. These are principally concerned with rapid ascent and precipitate descent. Changes in respiration are not noted at the height of from 1,000 to 2,000 meters. At from 2,000 to 5,000 meters, however, respirations become more rapid and the pilots may experience air hunger, which results in deepened respirations, at times in panting. At this height, in consequence of increased ventilation of the lungs, there results, according to some observers, acidosis of the blood and, according to others, alkalosis in consequence of diminution of carbon dioxide and a disturbance in the acid-base equilibrium which determines hydrogen ion concentration. The Italian school has demonstrated this by showing a loss of alkalinity on the part of the kidneys rather than by establishing a state of true acidosis by the presence of an acid substance in the blood. Acceleration of the pulse at a high altitude may result from lowering of barometric pressure or from emotion. A sense of painful constriction in the cardiac region with tachycardia and congestion of the face is sometimes noted in a rapid descent. The blood pressure increases in an ascent and decreases in descent. According to some observers, arterial hypotension is the result of the excitation of the labyrinth reflexly producing vasodilatation. Anorexia, nausea and vomiting, a state resembling seasickness, as well as dryness of the mouth are experienced by some. Hemorrhages do not occur at these altitudes. Mild auditory and visual disturbances frequently occur. Mental effects are of great importance in aviation. It is a common observation that concentration, ability to judge and

the faculty of decision diminish strikingly at altitudes of 7,000 and higher. Some of these effects are not unlike those caused by alcohol. Among the effects noted after a flight are: fibrillary tremors of the extremities, fast pulse, a sense of fulness in the ears, severe headache which may persist for forty-eight hours, nervousness, urinary suppression, restlessness and insomnia. The examination of the aspirants consists of the following: (1) somatic examination; (2) examination of eyesight; (3) examination of the ear, nose, throat and hearing; (4) examination of the vestibular apparatus and of the sense of equilibrium and motion; (5) psychic examination, including attention, memory, discrimination, speed and extension of perception; (6) determination of the time of reaction and selection; (7) examination of emotions; (8) examination of muscle sense and (9) examination of resistance to lowered barometric pressure.

IMPORTANCE OF RELATIONSHIP OF STATIC AND DYNAMIC DATA TO CONSTITUTIONAL VIGOR IN SELECTION OF AIR PILOTS. GIUSEPPI SGARBI, Arch. di anthrop. crim. **47**:792, 1927.

The author considers the determination of dynamic qualities of the cardiovascular system, as practiced in the United States, as an insufficient criterion because, in his opinion, the pulmonary apparatus is of greater importance to the aviator than the cardiovascular. For this reason he proposes a new index which he calls a thoracopulmonary index. This is the resultant of six measurements: (1) index of the thoracic cavity obtained by multiplying the anteroposterior, transverse and sternal diameters; (2) vital capacity estimated on the basis of ten respirations by the apparatus of Verdin; (3) respiratory force determined with the mask of Pech; (4) the same obtained with nasal respiration only; (5) tonicity of the diaphragm and of the respiratory muscles obtained with forced voluntary apnea following a single prolonged inspiration. The complete examination includes the study of the particular type, the state of the sympathetic and parasympathetic nervous systems, of the character, temperament, of both cardiovascular and thoracopulmonary indexes, structural index, weight index and of the particular physiognomy.

PERSISTENT MILK SECRETION IN A MAN. H. HAENEL, München. med. Wchnschr. **75**:261, 1928.

A man, aged 43, with suggestive secondary hermaphroditic symptoms, since his twenty-first year had had an uninterrupted secretion of milk in both mammae which continued undiminished four years after the cessation of sex functions.

AUTHOR'S SUMMARY.

THE HEREDITARY RELATIONS OF THE DIFFERENT FORMS OF CONGENITAL COLOR BLINDNESS. GEORG H. M. WAALER, Acta Ophth. **6**:309, 1927.

Among 18,121 school children of Oslo, 9,049 boys and 9,072 girls, about 8 per cent of the boys were color blind (1 per cent each for those protanopic, deuteranopic and protanomalopic, and 5 per cent deuteranomalopic), and about 0.5 per cent of the girls were color blind, mostly deuteranomalopic. Many normal and color blind relatives of the color blind school children were also examined and an analysis of the inheritance attempted on the basis of the allelomorphic hypothesis, with special discussion of the probable relation of the allelomorphs to the X chromosome and of the possible influence of other modifying factors. That one pair of allelomorphs determines protanopia and protanomalopia and another pair determines deuteranopia and deuteranomalopia and that the last named of each pair is dominant to the first, but that this dominance and the dominance of the normal allelomorph (color blindness generally being accepted as a recessive sex-linked character) are not invariable were some of the chief considerations.

AUTHOR'S SUMMARY.

Pathologic Anatomy

ANATOMICAL STUDIES ON THE CORONARY ARTERIES AND THEIR BRANCHES. M. A. KUGEL, Am. Heart J. **3**:260, 1928.

A large anastomotic blood vessel which runs in the auricular walls and links up the left and right coronary arteries has been described. This vessel is constant in its occurrence, though subject to variations in course. It supplies branches to the aortic cusp of the mitral valve, to the aortic valve (when blood vessels are found in these sites), to the commissures and to the base of the aorta. Its intimate relationship with these structures suggests that it may play a part in the pathogenesis of mitral and aortic lesions, commissural lesions and possibly lesions at the root of the aorta.

AUTHOR'S SUMMARY.

EXPERIMENTAL MYOCARDITIS. SCOTT JOHNSON and WALTER J. SIEBERT, Am. Heart J. **3**:279, 1928.

One injection of 0.025 Gm. of caffeine sodium benzoate with 0.2 cc. of epinephrine caused myocarditic lesions in practically all of the rabbits. The most frequent site of this lesion is in the papillary muscles of the left ventricle. Next in frequency are the myocardium of the left ventricle at the upper half of the anterior aspect, which in some cases encroaches on the myocardium of the left auricle, then the upper half of the posterior aspect of the left ventricle. The lesions appear a few days after the injections and consist of (*a*) interstitial edema; (*b*) hypertrophy of the muscle fibers and nuclei; (*c*) degenerative changes in the muscle fibers, which vary in severity from loss of cross striations and increase in intensity of the longitudinal striations, to granulation, vacuolization and solution of the muscle fibers; (*d*) proliferation of the connective tissue; (*e*) proliferation of the endocardium adjacent to the myocardial lesion and hemorrhages into the endocardium; (*f*) pericarditis, and (*g*) fatty degeneration of the myocardial cells in and immediately around the myocarditic lesion. The lesions are most marked from twelve to twenty-one days after the injections and are progressively less evident both grossly and microscopically at later periods.

AUTHORS' SUMMARY.

NECROSIS OF THE MALPIGHIAN BODIES OF THE SPLEEN. NORBERT ENZER, Am. J. Path. **2**:511, 1926.

There are seven earlier cases, four due to arteriosclerosis and three to proliferation of endothelium and thrombosis in eclampsia (2) and pneumonia (1). The example reported occurred in pernicious anemia; the necrosis was limited to malpighian bodies and is ascribed to proliferation of sinus endothelium.

THE SIGNIFICANCE OF GIANT CELLS IN THE INTRADERMAL TUBERCULIN REACTION. FRED W. STEWART and C. P. RHOADS, Am. J. Path. **2**:571, 1926.

The giant cells in the intradermal tuberculin focus are regarded as nonspecific and as developed in response to necrosis, particularly of fat tissue.

THE PATHOLOGY OF BILHARZIASIS. HARRY S. HUTCHISON, Am. J. Path. **4**:1, 1928.

The presence of the parasites and their eggs in the tissues causes a simple inflammatory reaction, which may be followed in nonsuperficial tissues by ulceration due to secondary bacterial infection. In the deeper tissues, abscesses do not occur, as a rule, but the characteristic bilharzial pseudotubercle, with eventual fibrosis, develops. There is evidence that the parasite produces harmful substances

in the body of its host, but the nature of this substance or substances is not established. It may concern the results of splitting of protein rather than production of toxin. The digestion and removal of the embryos is attended with a secondary anemia, slight leukocytosis and eosinophilia. Pigment similar to that in the enteric canal of the parasites is deposited, particularly in the spleen and liver. With extracts of the livers of infected snails as antigen, Fairley obtained a specific complement fixation in 88 per cent of the cases.

THE CIRCULATION IN THE KIDNEY WITH ROENTGENOGRAPHIC VISUALIZATION OF THE ARTERIAL TREE, INCLUDING THE GLOMERULI. RALPH S. GRAHAM, Am. J. Path. **4**:17, 1928.

Injecting the renal vessels with radiopaque suspension followed by roentgenography of the kidney can be readily adapted to the material obtained at autopsy without interfering with the other examinations. Results correspond well with the accepted conception of the arterial distribution in the normal kidney. Severe arteriosclerosis is marked by dilatations and constrictions of the vessels, wider interlobar and arcuate arteries and fewer, shorter and tortuous interlobular arteries and decrease in the number of glomeruli. As the kidney contracts, the arterial tree in the roentgenogram suggests a gnarled oak rather than a graceful elm. When present, the vascular changes in syphilis appear to be similar to those of arteriosclerosis. This method is of value in the study of thrombosis and infarcts. In acute degenerative changes, acute nephritis and passive congestion, the injection does not give a distinctive picture.

THE ETIOLOGY AND PATHOLOGY OF PYELITIS, URETERITIS AND CYSTITIS CYSTICA. HARRY D. MORSE, Am. J. Path. **4**:33, 1928.

Glandular structures are not normally found in the urinary tract above the trigone of the bladder. Epithelial buds, cell nests and cysts are not normally found in the urinary tract. Cysts of the urinary tract are formed from the epithelial nests of von Brunn. The epithelial buds and cell nests of von Brunn are inflammatory in nature. Microscopically, epithelial buds, cell nests and cysts are present in the majority of persons more than 20 years of age. This study does not reveal evidence to support the secretory theory of the formation of these cysts. The cysts are formed by degeneration of the central cells of the epithelial cell nests.

AUTHOR'S SUMMARY.

AN EPITHELIAL CYST OF THE HYPOPHYSIS. MARJORIE FULSTOW, Am. J. Path. **4**:87, 1928.

A cyst containing gelatinous material and lined by stratified squamous epithelium with papillary projections was situated between the anterior and posterior lobes of the pituitary. In places the lining presented ciliated cells, but hair follicles or epithelial pearls were not found. The cyst probably originated from the hypophysial duct. The symptoms — disturbance of heat regulation, polyuria and thirst — may have been due to pressure at the base of the brain. Several microscopic cysts in the white matter of the left occipital lobe were also found.

ABDOMINAL DEEP THERAPY INJURIES WITH REPORT OF NECROPSY FINDINGS IN A FATAL CASE. C. F. BALL, Am. J. Roentgenol. & Radium Therapy **13**:220, 1925.

After removal of the uterus on account of carcinoma, energetic treatment with roentgen rays was practiced, followed by steadily increasing weakness. After death, there was severe degeneration of the parts treated, in the muscles as well as in the small intestine in which the mucosa was destroyed. The structures lying on the sacral promontory were especially involved, owing, it is thought, to secondary irradiation from the bone.

SYPHILIS OF THE LUNG. R. C. KIRKWOOD, Am. Rev. Tuberc. **13**:220, 1926.

Kirkwood has seen a number of cases diagnosed as pulmonary tuberculosis, but which proved to be pulmonary syphilis. It is his feeling that syphilis of the lungs occurs more frequently than the literature on the subject suggests. Pathologically, he classifies the lesion found in pulmonary syphilis into three types: (1) diffuse peribronchial fibrosis, with bronchiectasis at one or both bases (the so-called "fibrous induration"); (2) gumma, single or multiple, and (3) consolidation and catarrh, the so-called "bronchopneumonic" type. He affirms that in acquired syphilis, at least, the diffuse fibroid induration type is most common. In congenital syphilis, gummas are probably most frequently seen.

B. M. FRIED.

AORTITIS ASSOCIATED WITH SYSTEMIC INFECTIONS. M. H. BROWN, Ann. Clin. Med. **5**:353, 1926.

Brown studied the aortas of twenty-nine persons who had died of some systemic infection. The characteristic lesion is a nonsuppurative inflammatory reaction about the vasa vasorum of the outer half of the media, with necrosis of the adjacent muscle cells and elastic fibers. The most marked reactions occurred in acute rheumatic fever and might be mistaken for the early stages of syphilitic aortitis, except that syphilitic mesaortitis has a greater lymphoid infiltration, extending to the intima; the nodular endarteritis is more marked and gummy necrosis is sometimes present in syphilis. Not a few of the inflammatory lesions in the aorta associated with acute infections can be recognized clinically.

WALTER M. SIMPSON.

THE WEIGHT OF THE HEART IN SCHIZOPHRENIA AND IN OTHER MENTAL DISORDERS. MARJORIE DULSTON, Arch. Neurol. & Psychiat. **16**:620, 1926.

Hearts of psychotic patients grouped together undergo the same changes in weight with increasing age as to those of sane persons. In schizophrenia, 49 per cent of men and 66 per cent of women had hearts weighing less than 300 Gm., while in a sane group, 21 per cent of men and 51 per cent of women had hearts weighing less than 300 Gm.

ROY GRINKER.

A CASE OF AMAUROTIC FAMILY IDIOCY, LATE INFANTILE TYPE (BIELSCHOWSKY) WITH CLINICAL PICTURE OF DECEREBRATE RIGIDITY. GEORGE B. HASSIN, Arch. Neurol. & Psychiat. **16**:708, 1926.

The author found typical changes of amaurotic idiocy including diffuse vacuolation of the ganglion cells containing amorphous deposits, rarefaction of medullary nerve fibers, atrophy of all cerebellar layers and marked degeneration of the deeper layers of the occipital lobe and of the ganglion cells of the nucleus Ruber. There was a lipoid accumulation in the adventitial spaces of the blood vessels.

ROY GRINKER.

THROMBOSIS OF THE SPINAL VESSELS IN SUDDEN SYPHILITIC PARAPLEGIA. M. F. CHUNG, Arch. Neurol. & Psychiat. **16**:716, 1926.

In two cases of sudden spinal paraplegia in syphilitic patients the cause was thrombosis of one or more important spinal vessels with myelomalacia. The cord infarcts were wedge-shaped when at the periphery and ellipsoid when intramedullary. Thrombosis may take place in arteries or veins with little

meningitis about them. The frequency of the involvement of the posterior aspect of the cord is explained by the smaller size of the vessels and their vulnerability to the attack of the syphilitic virus.

ROY GRINKER.

ANEURYSMS OF CEREBRAL VESSELS, CLINICAL MANIFESTATIONS AND PATHOLOGY. H. L. PARKER, Arch. Neurol. & Psychiat. **16**:728, 1926.

Four cases are reported; arteriosclerosis was the cause of the aneurysm in one, endocarditis with embolism in one and congenital weakness of the arterial wall in two. Congenital weakness of the wall of a cerebral artery resulting in aneurysm was associated in one case with a congenital closure of the aorta at the origin of the fetal ductus arteriosus.

ROY GRINKER.

PATHOLOGIC CHANGES IN HUNTINGTON'S CHOREA WITH SPECIAL REFERENCE TO THE CORPUS STRIATUM. CHARLES B. DUNLAP, Arch. Neurol. & Psychiat. **18**:867, 1927.

A careful microscopic study was made of the corpus striatum and the other parts of the brain. The number of cells in a given area of each putamen, globus pallidus and caudate nucleus were counted. A definite decrease was found in the number and character of the cells in the putamen and caudate nucleus in cases of Huntington's chorea. Degenerative destructive process involving the nerve cells of the putamen and caudate nucleus and an atrophic process affecting the nerve cells and fibers of the cerebral hemispheres were found, accompanied by a striking shrinkage in volume and mass of both gray and white matter of the hemispheres. If these changes are found, one can safely make a postmortem diagnosis of Huntington's chorea.

T. T. STONE.

ENCEPHALITIS PERIAXIALIS DIFFUSA (SCHILDER): A CASE REPORT WITH CLINICAL AND ANATOMIC STUDIES. GEORGE SCHALENBRAND, Arch. Neurol. & Psychiat. **18**:944, 1927.

This case occurred in a school girl, aged 14, who died after illness of three months' duration. A diagnosis of Schilder's disease was made premortem. The brain showed widespread softening and disintegration of the white matter of both hemispheres, the gray matter in general being spared. The process involved the corpus callosum and extended downward as far as the midbrain and the optic chiasm. The areas of severe degeneration showed a complete destruction of the myelin which was taken up by scavenger cells of microglial origin. The axis cylinders were partially preserved. The oligodengroglia had entirely disappeared. The neuroglia had hypertrophied in number and in size of the cells, and formed a thick fibrous network. There was an abnormal filling of the blood vessels and a mucoid degeneration of the oligodendroglia in the less involved areas. The perivascular spaces were enlarged and were filled with scavenger cells and a few lymphocytes. Connective tissue scar was formed in the regions of the severest destruction where there was also degeneration of the astrocytes into polymorphonuclear forms without prolongations.

T. T. STONE.

THE PATHOLOGIC CHANGES OF AMYOTONIA CONGENITA: A DISCUSSION OF ITS RELATION TO INFANTILE PROGRESSIVE MUSCULAR ATROPHY. ROY R. GRINKER, Arch. Neurol. & Psychiat. **18**:982, 1927.

The author reports a case of amyotonia congenita (Oppenheim) in a girl, aged 6 months, who could not move her legs and arms well and had marked paresis of the lower extremities and less of the upper. The involved muscles were soft and flaccid and all the deep reflexes were absent.

Anatomically, the essential changes were in the lower motor neuron, in which was a dearth of cells of the anterior horns; those present were either small, rounded and poor in chromatin or long and fusiform. There was a definite absence of glial reaction, scar formation or vascular changes. All the changes suggested a developmental defect. Hypertrophic or large cells with thick processes rich in neurofibrils were present also. The skeletal muscles showed a decrease in the size of the fiber which contained all the markings of the normal muscle. In many places normal muscle fibers were seen merging into small muscle fibers. The conclusions were that there is a definite anatomic difference between amyotonia congenita and Werding-Hoffman type of progressive muscular atrophy. The Werding-Hoffman type shows an actual degeneration of the ganglion cells and neuronophagia. The fundamental difference in the two groups is probably only a matter of the time at which the ganglion cells are affected.

T. T. STONE.

PNEUMOCEPHALUS. W. F. DANDY, Arch. Surg. **12**:949 (May) 1926.

The author's summary adequately covers the chief points in the article: 1. Pneumocephalus may follow any artificial communication between the paranasal or mastoid sinuses and the cranial chamber. It may also result from infections of gas producing organisms. 2. Sneezing, coughing, straining or swallowing is necessary to force the air through a bony and dural defect into the cranial chamber. 3. The intracranial air may be subdivided into four varieties according to location: (1) subarachnoid, (2) subdural, (3) intracerebral, (4) intraventricular. The intracerebral variety appears to be the most frequent. 4. The symptoms are mainly those of increased intracranial pressure, but rhinorrhea after sneezing or change of position is almost pathognomonic. A discharge of cerebrospinal fluid is usually present. 5. The absolute diagnosis is made by the roentgen ray. 6. Death results from infection and pressure in about 40 per cent of the cases.

N. ENZER.

POSTOPERATIVE PULMONARY ATELECTASIS. W. J. M. SCOTT and J. J. JOELSON, Arch. Surg. **15**:855, 1927.

The authors report a case in which postoperative atelectasis, limited to one lung, developed after operations on each kidney. The lung involved was generally in a dependent position. The authors collected reports of nine other cases in which the same type of collapse occurred, in which the patient had been lying on the involved side. They believe that posture determines the localization of the process, but that the initial factor is probably reflex in origin.

N. ENZER.

THE CHANGES IN THE THYROID PRODUCED BY IODINE IN EXOPHTHALMIC GOITER. W. W. SAGER, Arch. Surg. **15**:878, 1927.

One hundred specimens typical of exophthalmic goiter were compared with 100 specimens removed after treatment with compound solution of iodine (with Lugol's solution). An increase in colloid and a decrease in hypertrophy and hyperplasia in the thyroid gland occurred after the administration of iodine. There was probably a decrease in the amount of connective tissue and in the size of the arteries and capillaries. Iodine does not have any effect on the number of lymphocytes present.

N. ENZER.

PNEUMOCEPHALUS OF BACTERIAL ORIGIN. W. E. DANDY, Arch. Surg. **15**:913, 1927.

This interesting case of pneumocephalus occurred in a boy, aged 6 years, following a mastoid operation. About three weeks after the operation, the clinical

signs indicated the possibility of an abscess of the temporal lobe. Exploration revealed an abscess which was tapped, but symptoms of increased intracranial tension returned and tapping was done about every two days, until finally a permanent drain was put in for five days. A roentgen-ray examination revealed a large air shadow in the temporal lobe, and when the abscess was tapped, bubbles of air escaped through the needle. Cultures of the pus revealed a gram-negative bacillus, which produced gas in dextrose and maltose, was nonmotile and nonspore-bearing and which did not grow aerobically. A brief report of two cases in the literature due to *B. welchii* is added.

N. Enzer.

The Internal Callus. L. W. Ely, Arch. Surg. **15**:936, 1927.

When a hole is bored into the cortex of a long bone of an animal, it becomes filled with fibrous tissue which is continuous with the periosteum and often extends well down into the marrow canal. Instead of forming a barrier to bony union, this formation of fibrous tissue is evidently a step in the healing process. In it bone trabeculae form irregularly. Sometimes they are most numerous near the surface of the cortex, sometimes in the hole and occasionally in the marrow beneath the hole.

N. Enzer.

The Rôle of Aberrant Vessels in the Production of Hydronephrosis. Charles P. Mathé, J. Urol. **19**:211, 1928.

The renal blood vessels are irregular in their distribution and present numerous varieties and anomalies. This is explained by the fact that there may be multiple renal arteries and veins with every conceivable type of branching, depending on the selection of the channels from the embryonic periaortic plexus. Retention of a portion of the normal renal vascular relations of the embryo before the ascent of the mesonephros into the renal fossa may occur. The greater majority of anomalous vessels do not cause obstructive symptoms. In a certain percentage of cases, renal mobility may cause the ureter to sag or hang over a fixed support consisting of an aberrant vessel which leads to mechanical factors and causes obstruction and hydronephrosis.

Author's Summary.

Neoplasm of the Trigone Vesicae. Leon Herman, J. Urol. **19**:291, 1928.

A rare form of tumor probably arising from aberrant prostatic tubules in or below the trigonal musculature is described.

Rhabdomyosarcoma of the Urinary Bladder with Metastases. David W. MacKenzie and William H. Chase, J. Urol. **19**:314, 1928.

This tumor is primarily of interest on account of its extreme rarity in the urinary bladder and on account of its rapidly malignant characteristics. Although it is generally recognized that the rhabdomyosarcomas are the exception to the rule, that sarcomas spread by the blood stream, this case showed definite metastases in both lymph glands and portal circulation. Figure 6 demonstrates a portal space in the liver in which the portal vein is dilated and filled with undifferentiated tumor cells. The myoblastic nature of the tumor is well demonstrated in the lymph gland and portal metastases, yet it is hardly recognizable in the primary growth in the urinary bladder. Ewing quotes Eberth and Wolfensberger as having noted similar characteristics in lymph gland metastases. Histologic sections demonstrate numerous undifferentiated sacroblasts and scattered myoblasts in all stages of differentiation. The more mature the myoblastic cells, the less numerous they are in the portal metastases. Many of the reported cases of rhabdomyosarcomas have not shown actual striation of the myoblastic cells, so that the diagnosis has been less conclusive than in this case in which definite cross-striations of typical muscle cells have been conclusively demonstrated. The

extensive histologic search required in order to demonstrate beading and cross striations suggests that a certain number of undifferentiated malignant tumors may be mistaken for alveolar sarcomas, and hence the neoplasm may not be as rare as is indicated by the few cases reported.

AUTHORS' SUMMARY.

LEIOMYOMA OF THE URINARY BLADDER. A. R. STEVENS, J. Urol. **19**:329, 1928.

The tumor occurred in a man, aged 59. Histologically, it concerned a simple leiomyoma.

THE DISTRIBUTION OF THE ELASTIC TISSUE OF THE LUNG AND ITS SIGNIFICANCE. S. ROODHOUSE GLOYNE, Tubercle **9**:69, 1927.

The lungs possess three systems of elastic tissue: (1) a network beneath the pleural endothelium surrounding the lung; (2) a layer of elastic fibers in the walls of the arteries and veins, continuing out to the smallest capillaries, where some of the fibers spread out with the capillary network on the outside of the alveolar walls; (3) a strong network of longitudinal and circular elastic fibers in the walls of the bronchi, again extending out to the finest ramifications, where some of the fibers pass to the walls of the alveoli immediately external to the alveolar epithelium. It seems probable that in all these three systems, the elastic fibers are woven into a continuous network without interruptions, and that the three systems are closely interwoven together at certain points, viz., (*a*) beneath the pleura and (*b*) around the alveolar walls.

H. J. CORPER.

CYST OF THE THIRD VENTRICLE, WITH TOTAL DESTRUCTION OF THE INFUNDIBULUM AND WITHOUT HYPOPHYSEAL SYMPTOMS. L. FREY, Encéphale **22**:21, 1927.

A farmer, aged 26, felt a sudden pain in a tooth of the lower jaw, and the right cheek became swollen. Examination revealed anisocoria and nasal hemianopia of the right eye, with diminished vision and contraction of the temporal field on the same eye. In addition, there was an amaurosis of the left eye, with the inferior nasal quadrant preserved. Both fundi were normal. Horizontal nystagmus, strabismus convergens of the right eye and trismus were noted. The liquor showed a hypertension and a positive colloidal benzoin reaction. The sella turcica was roentgenographically normal. The blood showed a polyglobulia with 6,400,000 erythrocytes. After eight months the pain became unbearable, vomiting set in, and papilledema developed. At the same time, meningeal symptoms made their appearance. The diagnosis was tumor of the base of the brain. Before a decompression could be made, the patient died.

The autopsy showed the sella and hypophysis intact. A tumor, extending horizontally from the anterior wall of the third ventricle to the corpora mammillaria and reaching in vertical direction to the foramen of Monro (without occluding it), was pressing on the left chiasm. The infundibulum was completely destroyed. One process of the tumor projected toward the left gasserian ganglion. On section, a cyst was found, the outer sheath of which consisted of ependymal cells.

The author thinks that the cyst in question was secondary to a neoplasm (Erdheim cyst). But the spinal cells, characteristic of the Erdheim cysts (Stachel and Riffzellen), were not found. These cystic tumors originate from the epithelial cells which are normally found between the anterior lobe of the hypophysis and the infundibulum. They represent an embryonic rest of the pharyngohypophyseal canal. The fact that in the present case characteristic Erdheim cells were not found is perhaps due to the excessive cystic degeneration that had taken place. The hyperglobulia can perhaps be referred to pressure on the vegetative centers. Extrapyramidal lesions, which are to be expected in voluminous tumors of the third ventricle, were not noted.

In spite of the total destruction of the infundibulum, the only symptom pointing to this location was a disturbance of erection. Diabetes insipidus and dystrophia adiposogenitalis were absent.

A. LOW.

CYSTICERCUS RACEMOSUS OF THE BRAIN. G. GUILLAIN, I. BERTRAND, J. PERISSON and P. SCHMITE, Rev. neurol. **34**:433, 1927.

The patient, a man, aged 51, complained of diffuse pains in the head and in the lower extremities. Twenty-five years before the present complaint, he had had a series of from five to six generalized epileptic fits, and another series of about twelve fits ten years later. In the intervals he had been free from symptoms. Two years previously, the present condition, consisting of severe headache, an intense left sciatic neuralgia, occasional epileptic fits and mental disturbances, began to develop.

At autopsy, the brain showed a dense infiltration of the basilar meninges and a marked distention of the ventricles. The spinal meninges were likewise the seat of an intense infiltration which, however, was limited to the posterior aspect of the lower cervical and the entire dorsal region. In addition, whitish masses were found interspersed between the infiltrated areas which, on histologic examination, proved to be the shrunken cysts of cysticercosus racemosus.

The hydrocephalus and the concomitant signs of intracranial pressure find their explanation in the occlusion of the foramina of Luschka through the basilar meningitis. The selective localization of the parasitic cysts on the posterior aspect of the spinal cord accounts for the diffuse pains, and the invasion of the cauda equina for the sciatic neuralgia. An attempt is not made to explain the epileptiform attacks and the mental symptoms, and nothing is said about the histologic appearance of the parenchyma of the brain.

A. LOW.

CLASSIFICATION OF MENINGEAL TUMORS. G. ROUSSY and L. CORNIL, Rev. neurol. **35**:122, 1928.

After briefly reviewing Ribbert's and Cushing's views on meningeal tumors, the authors deal at length with Oberling's theories of the "neuro-epithelial" origin of the meningiomas. Oberling distinguishes between the internal meninx (the pia plus the inner membrane of the arachnoid) and the external meninx (the outer membrane of the arachnoid plus the dura.) The internal meninx is the analogon of Schwann's sheath, i. e., an ectodermal structure, related to the glia. It is this internal meninx which gives rise to the variety of meningeal tumors, known as endothelioma, fibroma, sarcoma and psammoma. All these various forms of tumors arise from the meningoblasts or those gliogenous cells of the internal meninx which are so closely related to the Schwann cells. Oberling, indeed, compiles all the meningeal tumors under the head of meningoblastomas.

According to this conception, the internal meninx and the sheath of Schwann belong to the same system, and both meningoblastomas and neurofibromas (Recklinghausen's disease) have an identical origin.

But this view would dispose of the dura as a factor in the formation of the meningeal tumors, and the justification of such a schematic and one-sided classification is doubted by the authors. Roussy and Cornil, then, proceed to present a classification of their own, dividing all the meningiomas into two main groups: the neuro-epithelial growths which arise from the internal meninx and, on the other hand, the fibromas and sarcomas which have their origin in the dura.

A. LOW.

ANATOMIC CLINICAL STUDY OF A CASE OF SYRINGOMYELIA WITH HYDROCEPHALUS. J. LHERMITTE and G. ROBIN, Rev. neurol. **35**:128, 1928.

Since the time of Schlesinger, it has been known that syringomyelia may occasionally be associated with hydrocephalus. The pathogenesis of this condition has always been obscure, and the authors think that the observations in their case may throw light on the problems involved.

A man, aged 32, two years after an accident developed disturbances of position and gait. One year later, disturbances of sensibility, muscular weakness and contractures were noted in the upper extremities. Gradulally, the cardinal symp-

toms of a typical syringomyelia appeared, and the patient died seven years after the initial trauma.

At autopsy, all ventricles were found markedly distended, the foramen of Monro greatly enlarged, and the whole length of the spinal cord invaded by central periependymal cavities.

Histologically, the spinal cord did not show the ordinary gliomatous formations, usually found in syringomyelia. Even when sufficient cord substance was preserved, as in the cervical and lumbosacral intumescences, glia proliferation of either miliar vascular changes was not observed, as is so commonly encountered in this disease. The main changes were found in the ependymal lining of the central canal, in the ependyma of the aqueductus sylvii and the ventricles. In the latter, there was a marked proliferation of the subependymal stratum gliosum fibrillare from which, in numerous places, papillae projected into the ventricular cavity. In the choroid plexus, there was, aside from the usual calcareous bodies, a coalescence of the tufts, an intense sclerosis of the perivascular tissue, a hyaline degeneration of the vessel walls and a distinct lymphocytic infiltration.

In their summary, the authors stress the etiologic importance of the trauma. The concussion, produced by the trauma, first damages the choroid plexus and the ependyma. The result is an overproduction of cerebrospinal fluid and, in consequence, hydrocephalus and syringomyelia.

A. Low.

Renal Calculosis and Malignant Epithelioma. Gian Carlo Peracchia, Tumori **2**:31, 1928.

The author reports a case of nephrolithiasis with pyonephrosis followed by metaplasia of the epithelium lining the renal pelvis and the development of a malignant epithelioma. The article contains a review of the literature and is accompanied by a roentgen-ray picture, a gross picture of the diseased kidney and several photomicrographs.

W. Ophüls.

Syphilis of the Stomach and General Paralysis. E. Straüsler, Monatschr. f. Psychiat. u. Neurol. **66**:117, 1927.

The author again insists that miliary gummas are found in cases of paresis. He contends that the diffuse cellular exudation is not a maligant process.

Roy Grinker.

The Central Nervous System in Congenital Spasticity. R. Ungar, Monatschr. f. Psychiat. u. Neurol. **66**:191, 1927.

The author describes a congenital diplegia revealing a failure of development of the Betz cells of the motor cortex and a diffuse glia change.

Roy Grinker.

The Significance of the Basophilic Cells of the Human Hypophysis. Kraus, Verhandl. d. deutsch. path. Gesellsch. **22**:196, 1927.

Basing their investigations on the observation of the degenerative changes of the basophilic cells of the hypophysis after destruction of the suprarenals, Kraus and Traube examined 225 hypophyses for determining the significance of the basophilic cells. They found that they were increased in number in persons of the hypersthenic type and in diseases most common among persons of this constitution frequently showing an increased blood pressure, such as constitutional obesity, essential hypertension, vascular sclerosis, genuine nephrocirrhosis, paresis, mesaortitis luetica, chronic alcoholism and secondary nephrocirrhosis. The basophilic cells were decreased in persons of the asthenic type usually possessing a decreased blood pressure and in diseases more common in persons of this type, such as diabetes accompanied by low blood pressure, tuberculosis and cancer. They suspect the existence of a causative relation between the number of basophilic cells and the apparatus regulating the blood pressure.

W. C. Hueper.

LIPOID OF SUPRARENAL AND THYROID GLANDS. WOLFF, Verhandl. d. deutsch. path. Gesellsch. **22**:201, 1927.

Wolff examined the suprarenal glands of white mice after feeding them with thyroxin or after injecting them subcutaneously with this substance. The lipoids disappeared first in the innermost zone of the fasciculata and later also from the median and outer layers, where they remained preserved for a long time. The lipoids in the reticularis usually remained unchanged, especially those in the paraxanthoma cells. Sometimes lipoids appeared in the glomerulosa in which they are absent normally. Similar changes of the lipoid content of the suprarenal glands could be produced by starvation, exclusive feeding with oily and lipoid substances and infections. The lipoid content was restored after the animals were fed for several days with normal food.

W. C. HUEPER.

EXPERIMENTS ON NEPHROCIRRHOSIS. M. SCHMIDTMANN, Verhandl. d. deutsch. path. Gesellsch. **22**:226, 1927.

Schmidtmann fed rabbits for some time with cholesterol and killed them after an interval of five or six months. She observed a marked atheromatosis, hypertrophy of the heart and nephrocirrhosis in some of the animals, while others remained absolutely normal. In the diseased animals transitions between harmless infiltrations of cholesterol of the tubular apparatus and those presenting extensive destruction were observed. These animals showed, moreover, a scantily developed lymphatic tissue of the spleen with atrophy of the pulp, arteriosclerosis of the follicular arteries with hyalinized, thickened media and thickened intima containing lipoid deposits. In subsequent experiments, rats were splenectomized and received a diet rich in cholesterol. All animals thus treated developed cirrhotic foci in the kidneys, while control animals did not show alterations or only those of minor extent. Similar results were obtained after feeding of lecithin. Animals splenectomized and fed with large quantities of cholesterol dissolved in oil died after several days with the symptoms of jaundice (acute atrophy of the liver). In the liver, necroses, fatty degeneration and hemorrhages were found. Hardly any lipoid was found in Kupffer's cells in contrast to the control animals. The degeneration of the tubular epithelium of the kidney was extensive. In splenectomized animals fed with cholesterol, the thickening of the intima is more pronounced than the deposition of lipoids, a condition which is reversed in normal animals given the same diet. Similar alterations can be obtained by other substances.

W. C. HUEPER.

THE ACTION OF BACTERIA AND OF BACTERIAL TOXINS ON SYMPATHETIC GANGLIA AND THEIR FUNCTION. A. LÄWEN and M. BIEBL, Ztschr. f. d. ges. exper. med. **57**:1, 1927.

Läwen and Biebl review the literature on morphologic changes found post mortem in various sympathetic ganglions, and investigate experimentally the relation between such lesions and functional disturbances attributed to the anatomic changes. The cervical sympathetic ganglion of the rabbit was used in the majority of the experiments. Cultures of staphylococci and of *B. coli* on cotton swabs applied to the area near the cervical sympathetic nerve caused paralysis of the pupillary dilator arc and of the vasoconstrictors of the rabbit's ear for a considerable length of time, if such cultures were placed in the immediate vicinity of the upper cervical sympathetic ganglion of the rabbit; there was little effect on either structure or function of the ganglion, which appeared to be well protected by its fibrous capsule. Any functional disturbance resulting could be referred to inflammatory processes in the tissues surrounding the ganglion, since morphologic changes were not found in the ganglion cells. Injection of cultures of staphylococci, *B. coli*, *B. pyocyaneus* and streptococci into the ganglions usually led to paralysis of the pupillary dilator arc, and in some instances, to paralysis of the vasoconstrictors of the ear. Histologic

examination showed degenerative changes of the ganglion cells as well as inflammatory infiltration within the ganglion; to these changes are attributed the disturbance of function. But there were a number of cases in which no functional disturbances were observed, in spite of well defined morphologic changes of the ganglion cells and of the stroma of the ganglion. These facts lead to the conclusion that it is not permissible invariably to assume disturbance of function of a ganglion when morphologic alterations are found.

BALDUIN LUCKE.

THE HISTOCHEMICAL DEMONSTRATION OF GOLD, AND A CONTRIBUTION TO THE QUESTION OF DISTRIBUTION AND EXCRETION OF SODIUM AUROTHIOSULPHATE IN THE HEALTHY AND TUBERCULOUS BODY. SHUSAKU KUROSU, Ztschr. f. d. ges. exper. Med. **57**:77, 1927.

The method for demonstrating gold in tissues depends on the general reaction: $2\,HAuCl_4 + 3\,SnCl_2 = Au + 3\,SnCl_4 + HCl$. Thin pieces of the tissue to be examined are fixed either in a mixture of 10 per cent formaldehyde and 5 per cent aqueous solution of stannous chloride ($SnCl_2$), or after fixation in formaldehyde are placed in the solution of stannous chloride. After from two to three days fixation, frozen sections or paraffin sections are made and placed in 5 per cent $SnCl_2$ solutions for from five to six days in the incubator at 37 C. or boiled for fifteen minutes. After washing, the sections are counterstained with carmine, safranine or hematoxylin. The gold appears as a brownish-black to black precipitate. This dark precipitate must be differentiated from melanin, formol precipitates, coal dust and iron pigment by appropriate control sections.

The distribution and excretion of sodium aurothiosulphate was studied in various healthy and tuberculous animals (mice, guinea-pigs, calves, monkeys) in the laboratory using the histochemical method for the demonstration of gold.

Deposition of gold was more pronounced in tuberculous organs than in normal organs. The gold particles were never in significant amount within the tuberculous lesions themselves, but were distributed throughout the adjacent nontuberculous tissue. Gold is excreted chiefly by the kidneys and the large intestines.

BALDUIN LUCKE.

STORAGE OF VITAL DYES IN THE RETICULO-ENDOTHELIAL SYSTEM. M. KAGAN, Ztschr. f. d. ges. exper. Med. **57**:111, 1927.

The object of the experiments was to determine the time of appearance of trypan-blue granules in the reticulo-endothelial cells of various organs after a single subcutaneous injection of this dye (0.5 cc. of a 0.5 per cent solution per ten grams of body weight). White mice were used, and killed after from fifteen minutes to seventy-two hours after injections. Trypan-blue granules appeared first in the proximal convoluted tubules of the kidney (two hours after injections). In the reticulo-endothelial cells storage was observed first in the Kupffer cells, and the reticulo-endothelial cells of the bone marrow and lymph nodes (from six to ten hours after injections); storage in the cells of the spleen and suprarenals occurred much later (from twenty to twenty-four hours after injections). In the histiocytes of the connective tissue, storage occurred earliest in the testes (six hours), and somewhat later in the urinary bladder, the stomach, intestines and in the capsules of various organs.

BALDUIN LUCKE.

ENDOMETRIOSIS OF THE RECTUM. P. R. MICHAËL, Nederl. Tijdschr. v. Geneesk. **71**:1846, 1927.

An endometrioma in the wall of the rectum is described. There was no ulceration. A significant symptom was increased discharge of blood with the feces at the time of menstruation.

Pathologic Chemistry

THE DISTRIBUTION OF ARSENIC IN THE TISSUES AFTER SERIAL ADMINISTRATION OF NEOARSPHENAMINE. F. P. UNDERHILL and A. DIMICK, Am. J. Physiol. **84**:56, 1928.

Dogs that had received from one to six doses of neoarsphenamine showed a distribution of arsenic in the tissues quite different from that occurring in chronic inorganic arsenic intoxication. The greatest deposition was in the kidneys, where there was a tendency for the quantity to increase significantly with the number of injections. The spleen also was a major depository, and behaved similarly to the kidney in regard to the effect of multiple doses. In the liver, the amount showed no relation to dosage, apparently varying with different animals. Very little was found in the brain. As an explanation of the greater storage of arsenic in the kidneys as compared with the liver, it is suggested that it is excreted in the bile with some rapidity, corresponding renal elimination being prevented by possible local injury there.

H. E. EGGERS.

BLOOD AND CEREBRO-SPINAL FLUID CHANGES AFTER INTRAVENOUS INJECTION OF HYPERTONIC SOLUTIONS. J. M. KINSMAN, R. G. SPURLING and F. JELSMA, Am. J. Physiol. **84**:165, 1928.

Following the intravenous injection of hypertonic salt solution into normal dogs and persons with cranial injuries, a transient rise in cerebrospinal fluid pressure was observed, which was followed by a consistent fall which varied with the amount and hypertonicity of the injected fluid. The administration caused a marked and immediate fall in the specific gravity of the blood and serum; the withdrawal of fluid from the tissues was caculated to range in man from 300 to 1,000 cc.; in dogs, from 100 to 900 cc. In the case of dextrose, a direct relationship was found between the amount of fluid withdrawn from the tissues and the molar concentration of this solute in the blood stream.

H. E. EGGERS.

CHEMICAL CHANGES IN THE BLOOD DURING FASTING AND SUBSEQUENT REFEEDING. S. MORGULIS, Am. J. Physiol. **84**:350, 1928.

In a study of the inorganic contents of the blood of fasting and refed dogs, it was found that the electrolytic content was maintained during inanition with little alteration. Striking changes appeared only during advanced stages of inanition. There then appeared a diminution of chlorides and of calcium, the former associated with a rise in the bicarbonate content of the blood, probably the effects of a toxicosis. The calcium was found during fasting only in the fluid portion of the blood, and its lowering may be due to a shifting of the globulin-albumin ratio. On refeeding, the inorganic blood content quickly returned to normal.

H. E. EGGERS.

CALCIUM AND ULTRA-VIOLET IRRADIATION. L. T. FAIRHALL, Am. J. Physiol. **84**:378, 1928.

In dogs irradiated with ultraviolet light over long periods of time, there was a slow increase of blood calcium. The effect was less with subsequent exposure, and could not be continued indefinitely. In irradiated rats on a low calcium diet, the calcium was deposited more slowly than in normal animals. The growth of these irradiated animals was apparently normal—in decided contrast to non-irradiated animals on a similar diet—but the average calcium content was only 50 per cent of that of normal rats of the same age. On a normal calcium diet, the irradiated rats had a somewhat higher calcium content than normal rats of the same age.

H. E. EGGERS.

THE ACTIVE PRINCIPLES OF THE POSTERIOR LOBE OF THE PITUITARY GLAND. OLIVER KAMM, T. B. ALDRICH, I. W. GROTE, L. W. ROWE and E. P. BUGBEE, J. Am. Chem. Soc. **50**:573, 1928.

The posterior lobe of the pituitary gland contains two important active principles: one which raises blood pressure and another which stimulates contraction of uterine muscle. A substantially complete separation of these two active principles has been accomplished by the employment of salting-out methods and, subsequently, by the use of appropriate solvents and precipitants. Solutions of these separated active principles have been recombined to form a pituitary extract identical with the original from which they were prepared, thus proving that no decomposition has taken place. The substantially pure pressor principle (β-hypophamine) has been obtained in the form of a white, stable, water-soluble power eighty times as potent as the International Standard Powdered Pituitary. The separated oxytocic principle (α-hypophamine) has been obtained in the form of a white, stable, water-soluble powder which is more than 150 times as potent as the International Standard Powdered Pituitary. The pressor principle has been shown to be responsible for the diuretic-antidiuretic action of pituitary extracts. The pressor principle when tested on animals for demonstration of pressor effects shows the development of tolerance which is characteristic of active pituitary extracts. It has been shown to possess no appreciable depressor action. Both active principles as basic bodies, presumably amines. . . . As a result of this preliminary work, the foundation is now laid for an investigation of the chemical nature of the separated hormones of the posterior lobe of the pituitary gland, together with a more exhaustive study of their pharmacologic properties.

AUTHORS' SUMMARY.

CHANGES IN THE PERCENTAGE OF CALCIUM AND PHOSPHORUS OF THE BLOOD FOLLOWING SECTION OF THE SYMPATHETIC, VAGUS NERVES AND SPINAL CORD. BENJAMIN N. BERG, ALFRED F. HESS and ELIZABETH SHERMAN, J. Exper. Med. **47**:105, 115, 1928.

When a splanchnic nerve or the celiac plexus was severed, a definite fall in serum calcium resulted, the level falling to 6 mg. per hundred cubic centimeters and remaining low for one or two weeks. Tetany, however, did not develop. The inorganic phosphate was slightly altered. On the other hand, when the vagi nerves were severed, the serum calcium rose. The equilibrium of both calcium and phosphorus was rendered less stable by the division of the sympathetic or the parasympathetic nerves. A marked rise and disturbance in equilibrium of the calcium in the blood was brought about by section of the spinal cord in the upper dorsal segment. This reaction, however, was not constant.

AUTHORS' SUMMARY.

THE NITROGEN CONTENT OF THE BILE AS A DIAGNOSTIC AID IN GALLBLADDER DISEASE. A. J. BOEKELMAN, Klin. Wchnschr. **7**:65, 1928.

Bile obtained from the gallbladder of normal adults with the duodenal tube contains less than 200 mg. of nitrogen per hundred cubic centimeters. In cholecystitis the nitrogen content is much greater, and in cholelithiasis it is variable.

R. BRENNWASSER.

POTASSIUM, CALCIUM AND SODIUM CONTENT OF BLOOD IN DIFFERENT FORMS OF EXPERIMENTALLY PRODUCED UREMIA. A. HARTWICH and G. HESSEL, Klin. Wchnschr. **7**:67, 1928.

Following complete nephrectomy, bilateral ligation of the ureters and anastomosis of a ureter and an iliac vein, there was a rise in the potassium content of the blood. There was decrease of the calcium and sodium chloride content in nephrectomy and in ligation of the ureters, while in a ureter vein anastomosis, the calcium and sodium chloride content remained high.

R. BRENNWASSER.

LIPASE OF SALIVA. K. SCHEER, Klin. Wchnschr. **7**:163, 1928.

Contrary to prevalent ideas, lipase occurs in saliva. It is destroyed at 65 C., is more active in the parotid secretion than in other secretions, and has an optimum actively at p_H 7.0. Calcium chloride and sodium oleate activate the lipase, and desiccation of the saliva concentrates it. The chief effect seems to be in cleansing the mouth.

E. F. HIRSCH.

Microbiology and Parasitology

THE DUODENAL FLORA IN ACHLORHYDRIA. L. RICEN, H. J. SEARS and L. M. DOWNING, Am. J. M. Sc. **175**:386, 1928.

Duodenal contents of fifteen subjects with normal gastric acidity and of thirty subjects with achlorhydria were obtained with ordinary sterile precautions. Plated out on blood agar the samples from the first group showed no bacterial growth, while those from the second were rich in organisms, many of them of the blood-destroying type.

S. D. SIMON.

FORMATION OF VESICAL CALCULI. B. H. HAGER and T. B. MAGATH, J. A. M. A. **90**:266, 1928.

In five cases of urinary lithiasis, *Proteus ammoniae* was isolated. Calculi can be experimentally produced in the bladder by *Proteus ammoniae* under favorable conditions. It is possible that deficiency of vitamin A is favorable to the implantation of *Proteus ammoniae*.

AUTHORS' SUMMARY.

POSTVACCINATION TETANUS AND ITS PREVENTION. CHARLES ARMSTRONG, J. A. M. A. **90**:738, 1928.

Epidemiologic evidence indicates that large insertions and the use of shields and dressings predispose to postvaccination tetanus in man.

Shields and dressings markedly favor the development of postvaccination tetanus in monkeys and rabbits vaccinated with a virus artificially contaminated with *B. tetani*.

A proper vaccination is defined as one in which the insertion is not more than one-eighth inch in its greatest diameter and which is made by some method that does not remove or destroy the epidermis. Such insertions, when treated openly, have never, as far as we are aware, been followed by postvaccination tetanus.

AUTHOR'S SUMMARY.

THE INGESTION OF RED BLOOD CORPUSCLES BY TRICHOMONAD FLAGELLATES. ROBERT HEGNER, J. A. M. A. **90**:741, 1928.

The conclusion is reached that red cells are accepted by the species of trichomonads used just as are other food particles in their environment, such as bacteria and organic débris, and that the habit of ingesting red cells cannot be used as evidence of pathogenicity.

AUTHOR'S SUMMARY.

STUDIES ON THE INACTIVATION OF VACCINE VIRUS AND THE ACTION OF CERTAIN SUBSTANCES UPON THE INFECTING POWER OF THE INACTIVATED VIRUS. F. DURAN REYNALS, J. Exper. Med. **47**:389, 1928.

Vaccine virus, obtained from testicular inoculation shows a high susceptibility to chloroform as compared with ether, toluene, 95 per cent alcohol and acetone. Vaccine virus, after treatment with an amount of chloroform sufficient to render it incapable or only barely capable of originating an eruption in the rabbit's skin, produces a characteristic eruption when injected with the supernatant fluid of embryonic tissue or sarcoma tissue "cultures" or kieselguhr, substances which are

markedly irritative to the rabbit's skin. Reactivation of the chloroformed vaccine virus is not possible when chloroform has been added to it in such quantity that the injection of large amounts of the treated virus fails to cause an eruption. Whenever reactivation has been accomplished, it has been possible to get a vaccine eruption of greater or less intensity by the injection of large amounts of the chloroformed vaccine alone. Embryo and chicken sarcoma "culture" fluids, when injected intradermally, make the skin susceptible to the localization of the virus introduced intravenously. The bearing of these experiments on the interpretation of Gye's theory of cancer causation is discussed.

AUTHOR'S SUMMARY.

ULCERATIVE TYPES AS DETERMINED BY INHERITANCE AND AS RELATED TO NATURAL RESISTANCE AGAINST TUBERCULOSIS IN GUINEA-PIGS. PAUL A. LEWIS and DOROTHY LOOMIS, J. Exper. Med. **47**:449, 1928.

Five families of strictly inbred guinea-pigs whose general resistance to experimental tuberculosis were previously determined by Wright and Lewis have been studied with reference to the characteristics of the local lesion produced by intracutaneous inoculation with the tubercle bacillus. It is found that there are clearly recognizable familial types based on the size and quality of the nodular lesion, the ulcerative lesion consecutive to this and the general effectiveness of the healing process when in evidence. In general, the qualities of lesion exhibited are such as to agree with the general resistance as previously determined, and it is believed that the qualities underlying the tissue reaction may be safely considered to be among the influential factors in the make-up of the natural resistance against tuberculosis. The differences in reaction are in part manifested against agents causing simple inflammation also, and hence must be designated as nonspecific with reference to the tubercle bacillus. There are definite indications of other "constitutional" differences in the character of the tissues and the general make-up of these families. The accumulated evidence from the study of the separate families and intercrosses between them is to the effect that the differences in question are transmitted by the blending type of inheritance and are therefore controlled by multiple unit characters. It is also suggested by the observations that certain of the significant characters are recessive in nature. It is of considerable interest that the observations agree very well with the older conception of an inherited, predisposing, constitutional diathesis as a significant factor in the incidence of tuberculosis.

CONTRIBUTION TO THE THERAPY OF ACUTE INFECTION. WILLIAM SUSMAN, Brit. J. Exper. Path. **8**:457, 1927.

The experiments fall into two classes, those made to ascertain: (1) the effect of injections of brain extract and of atropine on the immunization of rabbits as indicated by the agglutination titer to *B. typhosus*, (2) the effect of injections of brain extract in diminishing the mortality of mice when inoculated with pneumococcus type 1. Twelve rabbits were used, of which four were controls. Those inoculated were given a saline emulsion of a twenty-four hour, killed growth of *B. typhosus* standardized to 300 million per cubic centimeter. Four were not inoculated; eight were inoculated, of which four were given atropine and four an aqueous solution of brain extract. From the tables developed, the conclusion is drawn that when brain extract is used in conjunction with *B. typhosus* the immunization process is much accelerated and a much higher titer is produced. Atropine depresses the rate of agglutination formation. Other experiments were performed for the purpose of finding out whether brain extract is beneficial when mice are inoculated with pneumococcus type 1. Five hundred and twenty mice were inoculated. The results show that when mice are protected with brain extract, 51 per cent survive after all controls have died. The conclusion is drawn that the enhancing effect of the brain extract in the process of immunization may be due to the fact previously established experimentally that the extract stimulates the pulsation and probably the functional activity of the spleen.

IRVING SCHROTH.

IMMUNOLOGICAL AND SEROLOGICAL STUDIES ON THE VIRUSES OF FOWL-POX AND VACCINIA. G. M. FINDLAY, Proc. Roy. Soc. **102 B**:354, 1928.

No close relationship exists between the viruses of fowl-pox and vaccinia. Cross-immunity cannot be demonstrated in the hen. Antivaccinia serum from the hen or rabbit does not possess viricidial action on fowl-pox virus, and antifowl-pox serum from the hen does not have a viricidial effect on vaccinia virus. The virus of fowl-pox penetrates the Berkefeld filter more readily than that of vaccinia.

ARTHUR LOCKE.

CYTOLOGICAL STUDIES ON THE VIRUSES OF FOWL-POX AND VACCINIA. R. J. LUDFORD, Proc. Roy. Soc. **102 B**:406, 1928.

The virus bodies produced by vaccinia in the epidermal cells of the skin and cornea of the chick are identical with those produced by fowl-pox, but differ from those produced in the epidermal cells of the rat cornea in their possession of a covering of osmophil substance. The structure, manner of origin and development of the inclusions are discussed.

ARTHUR LOCKE.

SEDIMENTATION TEST IN INDIA WITH SPECIAL REFERENCE TO TUBERCULOSIS. C. FRIMODT-MÖLLER and P. V. BENJAMIN, Tubercle **9**:57, 1927.

The sedimentation test was performed on 500 persons in South India, 282 being tuberculous patients in a sanatorium. The tropical climate causes a higher rate of sedimentation than in the West. In tropical countries, the technic requires modification in that the test tube for keeping the mixed blood should not be used. The normal figure for men in South India, at 30 C. of the air, is 10 with a limit of 15, for women 15 with a limit of 20; expressed in percentage, it is equivalent to a reading of 17.0 and 25.5 mm. for men and to 25.5 and 34.0 mm. for women. The test is not of specific diagnostic value, being similar to fever in this respect. It cannot be used to determine activity or inactivity, but is a valuable aid in deciding activity when considered in due relation to the clinical symptoms. The prognostic value is considerable also in India. It is valuable in patients treated with artificial pneumothorax.

H. J. CORPER.

CONTRIBUTION TO THE STUDY OF HERPES VIRUS (MAROCAINE STRAIN). P. REMLINGER and J. BAILLY, Ann. de l'Inst. Pasteur **41**:1314, 1927.

To the species susceptible to the virus of herpes — rabbit, guinea-pig, mouse, rat, certain simians, man — may be added the cat, dog, pigeon, goose and hedgehog. Found to be refractory to intracerebral injections were the horse, mule, goat, hen, duck, common sparrow, buzzard, frog and land and water turtles. In refractory animals the virus does not immediately disappear (three days in turtles). The affinity of the virus for tissue derived from the ectoderm is not exclusive; subcutaneous cellular tissue particularly, in spite of its mesodermic origin, offers a good medium for the virus. Vaccination of rabbits is possible, though difficult; it parallels the vaccination of rabbits against the virus of rabies.

AUTHORS' CONCLUSIONS.

EXISTENCE OF MELIOIDOSIS IN COCHIN CHINA. R. PONS, Ann. de l'Inst. Pasteur **41**:1338, 1927.

It is considered that the organism of Whitmore and of Stanton and Fletcher is possibly related on the one hand to *B. mallei* and on the other hand to *B. pyocyaneus,* standing as an intermediate between the two.

M. S. MARSHALL.

THE PROPAGATION OF STREPTOCOCCUS SCARLATINAE. E. KOROBKOVA and S. MITINE, Rev. de microbiol. et epidemiol. **6**:474, 1927.

During the course of an epidemic of scarlet fever, the authors determined the incidence of hemolytic streptococci in the throats of patients with scarlet fever

at different periods after the onset, in the throats of healthy persons who had been in contact with patients who had scarlet fever, in the skin scales of patients convalescing from the disease and in the air of the rooms in which patients with scarlet fever were kept. The results were as follows:

1. Hemolytic streptococci were present in the throats of patients with scarlet fever from fourteen to twenty days after the onset in 55 per cent of the cases, from twenty-one to thirty days in 42 per cent and from thirty-one to forty days and longer in 38 per cent.

2. From the skin scales of patients convalescing from scarlet fever hemolytic streptococci were cultured in 37 per cent of the cases.

3. Among healthy persons living in contact with patients who had scarlet fever, 50 per cent harbored hemolytic streptococci.

4. In Petri plates placed at different distances from the patients and containing blood agar, after exposure to the air in the room of the patient for fifteen minutes, then incubated, there were on the average twenty-three colonies on four plates.

The hemolytic streptococci studied were capable of producing specific scarlatinal toxin.

P. S. Rhoads.

Meningococcus in Herpes of the Hands in a Case of Epidemic Meningitis. Alfred Plaut, Frankfürt. Ztschr. f. Pathol. **36**:18, 1928.

A boy, aged 14, developed a large patch of herpes on the dorsal part of the antithenar of the right hand on the ninth day of a typical epidemic of meningitis. Small pieces were excised and cut in series. The histologic picture was that of herpes, but meningococcus was found in it. Cultures from the contents of the herpes remained sterile, and so did the repeatedly made blood cultures, while the spinal fluid contained meningococci. Herpes bodies were not found. The meningococcus in the herpes has nothing to do with the formation of herpes; the skin lesion which is due to the meningococcus itself gives an entirely different picture (as described by Pick and Benda). The literature seems to contain no reports on the presence of the bacteria in the herpes eruptions occurring in infectious diseases. The herpes being localized mostly in the face, an opportunity for excision during life or after death is seldom given. In epidemic meningitis, extrafacial herpes is not so rare. Herpes on the hand is extremely rare. In atypical forms of meningitis, extrafacial herpes plays an important rôle (méningite herpétique). Theoretically, the contents of herpes in infectious diseases is capable of transmitting the disease.

Author's Summary.

Immunology

Attempts to Produce Skin Hypersensitiveness with Nonacid-Fast Tubercle Bacilli. C. H. Boissevain and S. W. Schaefer, Am. Rev. Tuberc. **16**:749, 1927.

Tubercle bacilli killed in the autoclave produce tuberculin hypersensitiveness after intraperitoneal injection, corroborating Petroff's observations. Extraction with ether, chloroform and petrolether does not deprive tubercle bacilli of their acid-fastness. The intraperitoneal injection of tubercle bacilli rendered nonacid-fast by grinding in a ball mill, by treatment with hydrochloric acid or by unsaturated fatty acids does not produce cutaneous hypersensitiveness to tuberculin. The authors consider the presence of tuberculoprotein, in a form in which it cannot be destroyed by the animal organism, as necessary for the production of hypersensitiveness. The anatomic tubercle is a sign of the presence of acid-fast bacilli, but is not directly responsible for the hypersensitiveness which is caused by the tuberculoprotein contained in the acid-fast bacilli.

H. J. Corper.

THE LOCAL IMMUNIZATION OF GUINEA-PIGS BY INTRACUTANEOUS INFECTION WITH TUBERCLE BACILLI OF LOW VIRULENCE. GEORGE G. ORNSTEIN and M. M. STEINBACH, Am. Rev. Tuberc. **17**:93, 1928.

Intracutaneous immunization confers a considerable degree of protection against intracutaneous reinfection with tubercle bacilli. Intracutaneous immunization confers a lesser degree of protection against subcutaneous reinfection, and it confers a greater degree of protection against reinfection than does subcutaneous immunization.

H. J. CORPER.

A METHOD FOR ESTIMATING THE POTENCY OF SMALLPOX VACCINE. JOHN N. FORCE and JAMES P. LEAKE, Bull. Hyg. Lab., U. S. P. H. S., no. 149, 1927.

The following criterion of potency is suggested: A smallpox vaccine of high potency, when diluted 1:1,000 should produce a confluent eruption on from 90 to 100 per cent of the vaccinated area on the back of a rabbit, and when diluted 1:3,000 the decrease in confluence should not be over 20 per cent. A vaccine satisfying this criterion should produce, in all previously unvaccinated human subjects, a circular vesicle measuring at least 7 mm. in diameter on the seventh day when applied, undiluted, to a circle of the exposed derma measuring 2 mm. in diameter.

AUTHORS' SUMMARY.

THE IMMUNOLOGIC RELATIONSHIP OF ALASTRIM AND MILD SMALLPOX. JAMES P. LEAKE and JOHN N. FORCE, Bull. Hyg. Lab., U. S. P. H. S., no. 149, 1927.

Experiments undertaken to investigate the immunologic relationship of the West Indian disease with that of the United States resulted as follows:

A vesicopapular eruption was regularly produced in monkeys, through three generations, by inoculation with material the sources of which were pustule contents from three Jamaican patients with alastrim. Crusts from a Haitian patient with the same disease produced a similar eruption in two monkeys. Crusts from two American patients with mild smallpox (District of Columbia and West Virginia) produced similar eruptions in monkeys through three generations.

Two monkeys successfully inoculated with alastrim were completely immune to vaccine virus thirteen and seventeen days later; the first of these was partially immune (gave a modified reaction or vaccinoid) to vaccine virus seventy-nine days after the inoculation with alastrim.

A monkey successfully vaccinated with vaccine virus was completely immune ten days later to alastrim and to inoculation with smallpox.

A monkey successfully inoculated with smallpox was completely immune twenty-days later to alastrim and to smallpox.

Another monkey successfully inoculated with smallpox was partially immune (gave a modified reaction or vaccinoid) to vaccine virus seventeen days later.

Two monkeys successfully inoculated with alastrim were completely immune to another inoculation of alastrium thirteen and twenty-two days later, respectively, and the first of these was completely immune to a third inoculation of alastrim and an inoculation with smallpox eighty-four days after the first inoculation.

Rabbits inoculated with alastrim showed some immunity to vaccine virus; those receiving two inoculations (directly with human material and with the first monkey generation) showed a higher degree of immunity than those inoculated once (with the second or third monkey generation). This immunity was not different from that shown by rabbits which had been inoculated with smallpox (second monkey generation). None of these rabbits showed marked lesions from their inoculations with smallpox or alastrim.

The fact that definite cross immunity exists between alastrim and mild smallpox and between alastrim and vaccine virus is additional evidence of the identity of alastrim and mild smallpox.

AUTHORS' SUMMARY.

ALLERGY TO NONHEMOLYTIC STREPTOCOCCI IN RELATION TO RHEUMATIC FEVER. HOMER F. SWIFT, C. L. DERICK and C. H. HITCHCOCK, J. A. M. A. **90**:906, 1928.

By injecting nonhemolytic streptococci in rabbits there can be created an allergic condition with respect to streptococci manifesting itself much like the allergy in animals injected with tubercle bacilli. This allergic state is not limited to the particular strain of streptococci used for the injection, but includes various streptococcal strains. In acute rheumatic fever hypersensitiveness to certain strains of *Streptococcus viridans* may be present. The state of the patient seems to be similar to the streptococcus allergy in rabbits. Probably focal infection may cause a sensitization or allergy of the tissues of the patient to a wide range of streptococci, and this allergy may play an important part in the pathogenesis of rheumatic fever.

THE DETERMINATION OF THE RATE OF ANTIBODY (PRECIPITIN) PRODUCTION IN RABBIT'S BLOOD BY THE METHOD OF "OPTIMAL PROPORTIONS." H. R. DEAN and R. A. WEBB, J. Path. & Bact. **31**:89, 1928.

The optimal proportions method for the measurement of the antibody content of a precipitating serum has been employed to follow the changes in the antibody content after the intravenous injection of horse serum into rabbits. Two rabbits were immunized with horse serum, and the subsequent progress of the antigen-antiserum ratio was determined by the titration of daily specimens of blood. The antibody content of each serum has been expressed in units, on the assumption that a unit of antibody is contained in the volume of antiserum which particulates most rapidly with 0.00001 cc. of normal horse serum. In both experiments the titer of the antiserum began to rise about the third day after the injection. After a sharp rise occupying from three to five days, the titer remained at a high level for from four to six days. This was followed by a sudden fall, which may have been the result of the loss of blood due to the taking of daily specimens. An attempt was made to follow the rise of antibody in the serum of a normal rabbit after a single injection of horse serum. Antibody could not be detected in this animal's serum until the tenth day after the injection. From the thirteenth to the twenty-second day, the titer remained fairly steady, when a sharp fall occurred. Antibody could not be detected after the thirty-fourth day. Attempts to repeat this experiment were unsuccessful. The optimal proportions method for the titration of antibody by precipitation has given satisfactory results in the case of relatively strong antiserums. With weak antiserums the method is difficult to apply, and the results have been unsatisfactory.

AUTHORS' SUMMARY.

VACCINATION OF THE NEW-BORN AGAINST TUBERCULOSIS WITH B.C.G. A. CALMETTE (with the collaboration of C. GUÉRIN, A. BOQUET and L. NÈGRE), Ann. de l'Inst. Pasteur. **42**:1, 1928.

The authors report the results of the use of B.C.G. in France from July 1, 1924, when the Pasteur Institute first made the vaccine available to the medical profession, to Dec. 1, 1927.

In the population at large, there were, from 1921 to 1926, from 8.5 to 11.6 deaths from all causes during the first year of life per hundred live births. The general mortality from tuberculosis was 0.16 per hundred. Different reports show that from 24 to 80 per cent of the children constantly exposed to tuberculosis die during the first year, presumably from tuberculosis. Deaths during the first year exceed deaths during subsequent years of childhood.

During the period of forty-one months, 52,772 children have been vaccinated in France. Of these, 6,219 were born of tuberculous mothers or were intimately and constantly exposed to tuberculosis infection. The number available for observation was 5,749, of whom 3,808 had been vaccinated for a year or less on Dec. 1, 1927. Of these, 118 are dead, and thirty-four are dying, probably with

tuberculosis. Thus the general mortality is 3.1 per hundred, or less than half the mortality of nonvaccinated nonexposed infants. The deaths from tuberculosis were 0.9 per hundred, as compared with from 24 to 80 per cent among unvaccinated infants.

On Dec. 1, 1927, 1,941 children, all exposed to infection, were available for study after having been vaccinated over one year (from one to three and one half years). Only four of twenty-one deaths which had occurred were probably due to tuberculosis. The general mortality was 1.2 per hundred (0.4 less than in the nonvaccinated nonexposed group), and the deaths from tuberculosis were 0.2 per hundred, all under 16 months of age. Thus in the 2-3.5 year group (917 children) the mortality from tuberculosis was zero. Of these, 298 had been revaccinated. The duration of immunity appears to be five years. In Seine-Inferieure, where the general and tuberculosis mortality rates are extremely high, the rates among vaccinated children were 6.7 and 0.5 per hundred, respectively. There were no deaths from tuberculosis among 19 deaths in 850 children in maternity hospitals and similar institutions.

There are no ill effects following the ingestion of the vaccine. Occasionally the lymphatic ganglions are swollen for a period of from two to three weeks, after which they disappear. At 6 months, 15 or 20 per cent give positive tuberculin reactions; at 18 months, 50 per cent; at 2 years, 60 per cent—all in children exposed to infection constantly, which may be a factor. The authors do not agree with the school believing that immunity to tuberculosis must be coincident with positive tuberculin reactions.

M. S. MARSHALL.

VACCINATION WITH B.C.G. IN ALGERIA, 1924-1927. E. SERGENT and H. ROUGEBIEF, Ann. de l'Inst. Pasteur **42**:35, 1928.

Between Nov. 4, 1924, and Dec. 1, 1927, 1,308 children were vaccinated. Of these, 564 were from 1 to 3 years of age on Dec. 1, 1927. It was possible to follow 208 of these children; sixty-two were constantly exposed to tuberculosis and 146 were not. Of the 208 children, thirty-four died during the interval, three from the exposed group and thirty-one from the supposedly nonexposed group. Only one of these deaths was due to tuberculosis, and in that case diagnosis was doubtful. It occurred in the nonexposed group. In unvaccinated children it is reported by another author that from 15 to 20 per cent of the deaths occurring in children from 0 to 30 months of age are due to tuberculosis in Algeria.

M. S. MARSHALL.

FLOCCULATION OF DIPHTHERIA AND TETANUS TOXINS WITH THEIR RESPECTIVE ANTITOXINS. S. SCHMIDT, Ann. de l'Inst. Pasteur. **42**:63, 1928.

In a certain mixture of tetanus toxin and antitoxin there is ordinarily formed a flocculation as reported by Ramon. This flocculation does not always appear with the same regularity and is not always indicative of the neutral point of mixture as is the case with diphtheria toxin and antitoxin.

The determination of the antigenic power of a toxin may, in certain cases, be effected by the flocculation method as indicated by Ramon and Descombey. In the author's experience, it was necessary to control each time the in vitro tests by injecting the flocculated mixture into animals.

The titration of antitetanus serum may be effected to a fair approximation with a great number of serums; the author agrees with the report of Abt and Erber.

Certain serums and certain toxins have several zones of flocculation. The method of titration in vitro may be employed (especially in the titration of toxins) only if one has found serums reacting in the same way with all toxins.

Certain antitetanus serums show a concordance between the rate of flocculation and the rate of neutralization. The rate of flocculation may indicate the avidity of antitoxtin for toxin, but this avidity is not indicative of the antitoxic potency of the serum and is determined by the person furnishing the serum.

AUTHOR'S SUMMARY.

IMPORTANCE OF KNOWLEDGE OF BLOOD GROUPING AND REPORT OF INVESTIGATIONS. H. LÜTZELER, Arch. f. Gynäk. **131**:171, 1927.

Following a somewhat cursory review of the main points of studies of blood grouping in man, in animals and in relation to diseases such as diphtheria, cancer, malaria and mental diseases, the author tabulates his own results in the grouping of about 700 patients with arteriosclerosis, tuberculosis, syphilis and cholelithiasis showing not more than a 4 per cent variation from the usual percentages. The conclusion was that there was no particular disposition of any blood group to any of these diseases.

EXPERIMENTAL INHIBITION OF TISSUE ANAPHYLAXIS. F. KLINGE, Verhandl. d. deutsch. path. Gesellsch. **22**:133, 1927.

Rabbits, dogs and guinea-pigs sensitized by injection of horse serum received before the second injection of serum a 2 per cent solution of trypan blue intravenously or intracutaneously at the place of the second injection of serum. Hyperergic inflammation was absent in 50 per cent of the animals that had been given injections. The amount of the injected trypan blue solution and the time of injection appeared to be important for the success. The interval between the injection of trypan blue and the second injection of serum has to be short, because the sensitiveness of the skin was absent only when the dye was still diffusely distributed in the tissue and not yet stored intracellularly. Similar results were obtained when injections were made into the knee joints of rabbits.

W. C. HUEPER.

PHYSIOCHEMICAL FACTORS IN INFECTION AND IMMUNE REACTIONS. CARL KRAUSPE, Verhandl. d. deutsch. path. Gesellsch. **22**:136, 1927.

Krauspe studied the significance of physicochemical factors on the infectiousness of bacteria. Colloidal silver solution injected into the peritoneal cavity was resorbed more quickly into the omentum, and a larger number of phagocytes was found in this organ when a 5 per cent solution of bile or sodium ricinolate solution was simultaneously injected; this changes the condition of the surface of the peritoneum. Experiments with staphylococci yielded similar results, especially when diluted solutions of bile were used to exclude any toxic effect of this substance. While suspensions of staphylococci injected intraperitoneally had sometimes little if any effect, a severe exudative peritonitis resulted when bile was simultaneously injected, in spite of the more marked cellular reaction and phagocytosis in the omentum. Krauspe concludes that the physicochemical qualities of a transudate or exudate and the action of fibrin as a strongly adsorptive substance may have some effect on the course of an infection. A reverse effect on an infection has the intravenous injection of surface active substances. They inhibit infection and may save the life. Cholesterol may act in this manner, and also immune serum with its low surface tension.

W. C. HUEPER.

PECULIARITIES OF LOBAR PNEUMONIA IN CHILDREN IN RELATION TO IMMUNITY REACTION OF EARLY CHILDHOOD. A. LAUCHE, Verhandl. d. deutsch. Path. Gesellsch. **22**:143, 1927.

Considering the similarity between experimental anaphylactic pneumonia and lobar pneumonia, Lauche interprets the pneumonic process as a hyperergic inflammatory reaction of the body sensitized against pneumococcus protein. The suddenness of the onset and the acuteness and intensity of the reaction point to a hypersensitiveness of the organism. The absence of lobar pneumonia during the first months of postfetal life is regarded as due to a lack of sensitization. Congenital lobar pneumonia is caused by a fetal sensitization transferred through the placenta and is of a passive nature, because the fetus in general does not produce antibodies readily on account of the insufficiently developed reticulo-

endothelial system at that time of life. Bronchopneumonia in infants is not caused by pneumococci but by streptococci and staphylococci. The involvement of both lungs in anaphylactic pneumonia is due to the higher sensitization of the body resulting in a more marked reaction than that present in lobar pneumonia, in which the body is sensitized to a lesser degree. The invasion of the tissue resulting in infection is caused by additional factors such as trauma. The infection in congenital pneumonia is usually not caused by way of the blood stream, but probably more frequently from aspirated contents of the infected genital tract.

W. C. HUEPER.

Tumors

NEUROGENIC SARCOMA. D. QUICK and M. CUTLER, Ann. Surg. **86**:810, 1927.

The malignant nature of tumors arising in the subcutaneous and intermuscular tissues of the arm, leg, popliteal space, wall of the chest and elsewhere is well illustrated. These tumors are nearly always classified as fibrosarcomas. Quick and Cutler prefer to consider them as neurogenic in origin and adopt Ewing's classification. They are in doubt concerning the origin of one group of these tumors, the myxosarcomas. There are some composed almost entirely of a mucinous matrix, which are radiosensitive. These are probably not neurogenic. But myxomatous degeneration in neurogenic fibrosarcoma is common, so that care must be taken in differentiating the latter from the true fascial myxosarcoma.

These tumors are generally multiple and movable. Local excision is usually resorted to, and is followed by recurrence, later by metastases. They are not sensitive to radium. In the thigh, they seem to be unusually malignant. Only two of fifteen patients survived.

The malignancy of these tumors is directly proportionate to their cellular content and scantiness of stroma. In fibrous, acellular tumors, local excision frequently cures, but in the cellular ones radiation before and after wide local excision seems to offer the best prognosis. Twenty per cent of the patients developed pulmonary metastases. In ten amputations, five of the patients died of metastases. The primary tumors were cellular. Radium, however, has been of benefit in recurrence of highly malignant tumors.

N. ENZER.

SOME FACTORS DETERMINING THE LOCALIZATION OF A CHICKEN TUMOR AGENT. RONALD D. MACKENZIE and ERNEST STURM, J. Exper. Med. **47**:345, 1928.

A localization out of the blood stream of the agent causing a chicken tumor, with the subsequent development of the growth, can be brought about in the breast muscle, by inducing in this tissue a reaction by such substances as scharlach r, tar, embryonic tissue and kieselguhr. Localization in the reaction tissue elicited by kieselguhr takes place relatively infrequently. The earlier stages of the reaction induced by these substances localize the tumor agent more regularly than the later stages of the reaction.

AUTHORS' SUMMARY.

THE EFFECT OF DIGESTS OF PURE PROTEINS ON CELL PROLIFERATION. LILLIAN E. BAKER and ALEXIS CARREL, J. Exper. Med. **47**:353, 1928.

The pepsin hydrolytic products of the pure proteins, crystalline egg albumin, crystalline edestin and purified fibrin are utilized by fibroblasts for their proliferation. It appears, therefore, that the growth of fibroblasts in fibrin digests and in the proteose of Witte's peptone is due to the split products of the protein itself and not to accompanying cellular constituents or other impurities. Preliminary denaturation of the protein, as carried out in these experiments, does not alter the nutritive properties of the digest. The digests of the pure proteins employed are deficient in certain substances and do not meet the entire nutritive requirement of the cells for an unlimited period of time. Some supplementary nutritive substances are present in fresh embryonic heart tissue. This circumstance explains

the growth of fibroblasts from fresh embryonic heart in digests which do not promote the growth of a pure strain of fibroblasts. Glycocoll and nucleic acid have been found to supplement the nutritive action of pure protein digests for sarcomatous fibroblasts and to increase greatly the length of life of the tissues. Vegetable proteins, as well as animal proteins, yield proteolytic products which promote the multiplication of fibroblasts.

AUTHORS' SUMMARY.

EFFECT OF LIVER AND PITUITARY DIGESTS ON THE PROLIFERATION OF SARCOMATOUS FIBROBLASTS OF THE RAT. LILLIAN E. BAKER and ALEXIS CARREL, J. Exper. Med. **47**:371, 1928.

A medium containing all the essential constituents for the cultivation in vitro of sarcomatous fibroblasts of the rat has been prepared by digesting calf liver and also the anterior lobe of the pituitary body with pepsin. The nutritive action of the pituitary digests is not altered by thorough extraction with ether. After a pure strain of sarcomatous fibroblasts had been cultivated for three months in a liver digest, its proliferative activity was as great as at the beginning of the experiment. The same was true of the colonies cultivated for one month in a digest of pituitary gland. The increase in the volume of the colonies which takes place in the digests is about as great as that produced by chick embryo juice. Normal chicken fibroblasts also proliferate in both digests, but they undergo fatty degeneration after a more or less prolonged period of cultivation.

AUTHORS' SUMMARY.

TUMORS OF THE RABBIT. CYRIL J. POLSON, J. Path. & Bact. **30**:603, 1927.

The author reports fourteen new tumors of the rabbit which, added to those already recorded, make a total list of sixty-six. The literature is reviewed to cover the past eleven years. The uterus is by far the most frequent site of tumor development in the rabbit; thirty of the sixty-six tumors had their origin there. Besides the fibromyomas, these are adenomas and adenocarcinomas. A detailed gross and histologic description is given of the fourteen new tumors, together with photomicrographs.

E. M. HALL.

MONOCYTES IN EXPERIMENTAL TUMOR PRODUCTION. E. HAAGEN, Deutsche med. Wchnschr. **54**:92, 1928.

The monocytes are probably the bearers of the tumor agent. Only monocytes obtained from the blood of sarcomatous chickens could be used in the successful transplantation of chicken sarcoma. Tumor transference was also carried out with the isolated monocytic ameboid cells from the sarcoma cultures, but not with the fibroblasts so obtained. Normal monocytes acquire the faculty of bringing about sarcoma formation in the chicken if they are treated beforehand with otherwise inactive sarcoma filtrates. With fibroblasts, tumors are not formed. If fresh or cultivated normal monocyte cultures are injected into chickens, together with very weak solutions of arsenous acids, a highly malignant sarcoma, such as never develops with fibroblasts, is obtained. The malignant element must be a chemical substance present only intracellularly in the active form, probably an enzyme, ferment or vitamin. It originates in exogenous irritation, which is also of chemical nature, but must play the rôle merely of activator or catalyzer.

EXPERIMENTAL MAMMARY CARCINOMA. B. FISCHER-WASELS, München. med. Wchnschr. **75**:73, 1928.

Scarlet red, dissolved in liquid petrolatum, was repeatedly injected into the mammae of female mice. After six months, thirty-two were still living. There was no tumor-like swelling. After twelve months, twenty-eight were living, one of which had in the injected mamma a tumor the size of a cherry which proved to be an adenocarcinoma rich in cells. After seventeen months, eighteen of the mice were alive, four of which had adenocarcinomas from the size of a bean to

that of a cherry. In one of these mice there were extensive metastases of the carcinoma in the corresponding inguinal lymph glands; in two others there were pulmonary metastases. The longer the injury lasts, the more frequently does the forced regeneration go on to tumor formation.

THE CHOLESTEROL CONTENT OF THE BLOOD SERUM AFTER ROENTGEN IRRADIATION. R. HUBERT, Klin. Wchnschr. **7**:208, 1928.

After roentgen irradiation of carcinoma, there is a diminution of the cholesterol content of the serum while in other conditions there is a distinct increase following irradiation.

AUTHOR'S SUMMARY.

CHEMISTRY OF TUMORS. C. FAHRIG, Verhandl. d. deutsch. path. Gesellsch. **22**:71, 1927.

Fahrig, investigating the carbohydrate metabolism of tumor and normal tissue, determined their total content of carbohydrates, their buffer range and their ability to produce lactic acid. According to his observations, tumors and normal tissue do not differ considerably in their glycogen content. The same fact holds true in regard to the buffer range. All tumors and normal tissues examined with the exception of striated muscle tissue increase their glycolytic activity if dextrose and buffer substances are offered to them. The aerobic glycolysis which, according to Warburg, distinguishes tumor tissue from normal tissue is not an exclusive quality of blastomatous cells, because muscle tissue and lymphatic tissue also normally supply the blood with lactic acid. Fahrig asserts that the aerobic glycosis of tumor cells is caused by an insufficient blood supply and does not represent a specific cellular quality of tumor cells.

W. C. HUEPER.

EXPERIMENTS WITH ROUS' CHICKEN SARCOMA. C. STERNBERG, Verhandl. d. deutsch. path. Gesellsch. **22**:75, 1927.

Sternberg concludes from his experiments with filtrates of Rous' chicken sarcoma that its infectious nature is not proved, but that the transmission of the tumor by filtrates is caused through small parts of cells (partial bionts or plasomes), which can be activated when damaged by treatment with chloroform, by the addition not only of a "tumor culture," but of nonspecific substances, as extracts from chicken embryos, organs of chickens and guinea-pigs (Carrel, Murphy and others), and, according to Sternberg, also by the addition of sheep blood.

W. C. HUEPER.

EXPERIMENTAL EFFECTS ON THE GENESIS AND GROWTH OF TAR CARCINOMAS. R. JAFFÉ and A. ELIASSOW, Verhandl. d. deutsch. path. Gesellsch. **22**:78, 1927.

Mice were painted with a mixture of tar (carboneol) and cholesterol or lecithin, respectively; others were fed with these lipoid substances and painted with carboneol. The results showed that cholesterol mixed with carboneol inhibits or delays the formation of warts and carcinomas, while cholesterol fed produces the contrary effect. The effect of the lecithin was less marked. The increase of the proliferative activity of tumors by lipoid feeding is regarded as a result of a general metabolic disturbance. In another series of experiments in which rabbits were painted with a mixture of carboneol and ether a marked inhibition in the development of tumors was observed. But the rubbing of the ear to be painted with ether preceding the administration of the carboneol resulted apparently in an earlier and more regular production of tumors. Spontaneous regression of histologically carcinomatous formations and their transformation into simple warts was observed several times after suspension of the painting with tar. There seems to exist a difference between histologic and biologic malignancy. General metabolic disturbances are regarded as important in the genesis of carcinoma.

W. C. HUEPER.

NODULAR DERMATITIS WITH BASAL CELL PROLIFERATIONS DEVELOPING INTO CARCINOMA. H. HAMDI, Verhandl. d. deutsch. path. Gesellsch. **22**:90, 1927.

A case of chronic, small, nodular and papulous dermatitis is described which was histologically characterized by multiple proliferations of basal cells producing in later stages of the disease metastases in the axillary lymph nodes. The clinical course and manifestations resembled Bowen's dermatosis.

W. C. HUEPER.

CHRONIC INFLAMMATION AND CARCINOMA OF THE STOMACH. F. HENKE, Verhandl. d. deutsch. path. Gesellsch. **22**:93, 1927.

Henke substantiates from his own investigations the statement of Krompecher that linitis plastica of the stomach represents a peculiar type of small cellular carcinoma combined with a chronic productive inflammation. The presence of epithelial strands in the regionary lymph nodes facilitates the sometimes difficult diagnosis. Similar combinations of small cellular carcinoma and chronic inflammation are also observed in the gallbladder and the breast. Henke reports three cases of linitis plastica.

W. C. HUEPER.

TUMORS WITH LEUKEMIC CHANGES OF THE BLOOD. H. BORCHARDT, Verhandl. d. deutsch. path. Gesellsch. **22**:96, 1927.

Borchardt reports a case of lymphosarcoma in the later stages of which the symptoms of a lymphatic leukemia developed. The differential diagnosis between lymphosarcoma Kundrat-Paltauf, leukosarcoma Sternberg and leukemic lymphadenosis is discussed. The case reported cannot be classified as any of these diseases.

W. C. HUEPER.

HEMOBLASTOSES, BLASTOMAS AND INFECTIOUS DISEASES. E. MEYER, Verhandl. d. deutsch. path. Gesellsch. **22**:108, 1927.

The relations between leukemia, blastomas and infectious diseases in regard to the frequency of cellular changes in the blood, leukemic alterations in the tissues and unicentric and multicentric origin were studied by Meyer. He concludes from his investigations that the systemic involvements in hemoblastoses have a restricted significance, because many hemoblastoses do not produce changes in the hemopoietic organs, while similar alterations may be caused by other diseases. But the simultaneous occurrence of leukemic alterations in the blood and in these organs is by far more frequent in hemoblastoses, while infectious diseases produce in general only those in the blood and carcinosis of the bone marrow only those in the tissues. Acute leukemia cannot be regarded as a special type of infectious myelocytosis as Sternberg asserts. It may occur as a secondary disease following septic conditions and representing an indirect effect of them.

W. C. HUEPER.

THE ADSORPTION OF THE AGENT OF CHICKEN SARCOMA. F. PENTIMALLI, Verhandl. d. deutsch. path. Gesellsch. **22**:116, 1927.

The specific principle of a filtrate of Rous' chicken sarcoma is adsorbed to embryonal cells of the chicken when incubated together for one hour, while the filtrate then becomes inactive. These cells thus treated were injected, after washing, into the breast muscle of a chicken and produced teratomatous tumors. Regenerative cells and macrophages of the chicken did not adsorb the active principle when brought in contact with it.

W. C. HUEPER.

EXPERIMENTAL TUMORS PRODUCED BY CUTANEOUS INJECTION OF COAL-TAR AND PITYROL. T. SHIMODA, Acta Dermat. **10**:573, 1927.

By injecting coal-tar into one ear (rabbit) and tar from rice polishings into the other ear, each in 20 per cent suspension in olive oil, it was found that hyper-

keratosis and epithelial proliferation into the deeper tissues were more marked in the ear into which coal-tar was injected. Coal-tar also produced more changes in the subcutaneous tissue and in the cartilage of the ear than the tar from rice polishings.

Medicolegal Pathology

CEREBRAL CONCUSSION. G. G. MILLER, Arch. Surg. **14**:891, 1927.

This includes a review of the literature on cerebral concussion, contusion and compression with details of a few animal experiments, all definitely toward demonstrating that concussion is unaccompanied by demonstrable morphologic alterations. Trypan blue was injected intravenously into some animals on the day following and on each of two succeeding days after unconsciousness was produced by blows on the head. The absence of blue places in the brain was attributed to absence of injury. There is no mention of microscopic examinations of the brains of these or of other animals.

Concussion is said to be a result of disturbed equilibrium of the cells, and especially of cells of the brain cortex. Unconsciousness is immediate and tends to prompt spontaneous recovery. When death results from concussion, the respiratory center is the first of the vital centers to be paralyzed. This means, of course, that artificial respiration should be resorted to with severe concussion accompanied with serious respiratory disturbances. The effort of the author to demarcate concussion from contusion both clinically and anatomically is probably not applicable to what actually occurs, since hemorrhages and other lesions have been found microscopically frequently when gross lesions have been entirely absent.

E. R. LE COUNT.

IODINE POISONING FOLLOWING THE USE OF IODIZED OIL 40 PER CENT IN THE BRONCHI FOR DIAGNOSIS. E. RIST, F. HIRSCHBERG, G. E. H. ILL and J. RAULOT-LAPOINTE, Bull. et mém. Soc. méd. d. hôp. de Paris **43**:599, 1927.

Four days after two injections of iodized oil 40 per cent into the air passages, five days apart, an iodine rash appeared. A stenosis of the bronchi of the right lung, probably congenital, was found with dilatation of the left bronchi. There was no albuminuria, but edema of the face and pharynx developed, and these were like the toxic effects of potassium iodide. These symptoms continued about a week, and eight days after their onset considerable iodine was found in the urine.

E. R. LE COUNT.

A NEW DIAGNOSTIC CRITERIOM BASED ON THE INCISURE PRODUCED IN A WOUND BY THE WITHDRAWAL OF THE POINTED OR EDGED WEAPON. R. ROMANESE, Arch. di antrop. crim. **47**:944, 1927.

Romanese calls attention to the incisure that is commonly produced in a stabbing wound when a pointed or edged instrument is withdrawn, and states that it is possible from its site with respect to the main wound to conclude not only what the position of the blade was when the blow was struck, but also which hand (the right or the left) held the weapon. It will at times be valuable to know whether the assailant was right-handed or left-handed.

H. R. WOLCOTT.

DETERMINATION OF SPECIES FROM SMALL FRAGMENTS OF CALCINED BONES. GIORGIO CANUTO, Arch. di antrop. crim. **47**:948, 1927.

In connection with a suspected murder, twenty-two fragments of a bonelike substance, pieces of metal suspender buckles and a few rusty shoe nails were found in an old furnace on the property of a person suspected of the crime. The bonelike fragments were turned over to Dr. Canuto to determine whether they were

human bones. Canuto concluded after careful examination that: 1. The fragments are bones, for some present shafts easily recognized by the spongy tissue; others present smooth surfaces on which, even under weak magnification, the pores of the larger canals opening on the surface of the bones are visible. 2. The body of the organism to which the bones belong was chopped in pieces with a cutting or splitting instrument, for fine linear, rectilinear and parallel markings furnish evidence for the repeated strokes, which fact might be important for the reconstruction of a crime. 3. The bones have been exposed for a long time to the action of heat, as is shown by their exceedingly fragile condition and grayish color. 4. They are not human bones, for the greatest number of haversian canals found in human bones is from sixteen to eighteen per millimeter of bone substance, whereas various sections of these bones contain as high as thirty-eight, forty and even forty-three canals per millimeter. In addition, in all the fragments the canals are less than 10 microns in diameter, whereas the canals in human bones are much larger. 5. The bones in question are doubtless the bones of a pig.

H. R. WOLCOTT.

THE ACTION OF CARBON MONOXIDE ON THE ORGANISM. R. ROMANESE, Arch. di antrop. crim. **47**:959, 1927.

Romanese reaches the conclusion that the pathogenesis of the action of carbon monoxide on the human organism is not yet fully cleared up. The asphyctic theories, which explain clearly the physiopathology of the acute forms, do not serve to explain that of the syncopal forms, and it is only with difficulty that they can be adapted to explain that of the chronic forms. On the other hand, the toxic theories, which have been shown to be untenable in the acute and subacute forms, find possibly in the chronic types more plausible application, and may perhaps explain the reason, even in the acute forms, for the marked difference in the individual cases. The idea of reflex action may serve to explain the syncopal forms, in which neither the asphyctic nor the toxic theories are adequate. The action in the individual cases is due, in the author's opinion, to a combination of various phenomena. What decides the nature of the action is the predominance of one or the other phenomenon. Attempts to force an explanation by bringing the action under one schema are fruitless and pernicious.

H. R. WOLCOTT.

THE SPECTROMETRIC DETERMINATION OF CARBOXYHEMOGLOBIN. L. LATTES, Arch. di antrop. crim. **47**:1000, 1927.

Lattes performed a series of experiments to test the validity of Balthazard's claims with regard to the spectrometric determination of carboxyhemoglobin. He found that the coefficient of carbon monoxide poisoning (that is, the relation of the hemoglobin that has combined with carbon monoxide to the total amount of hemoglobin in the blood) cannot be determined as readily and as accurately as Balthazard claims it can, by means of the spectrometric measurement of the position of the alpha band of the absorption spectrum of the blood, since such position is not solely the function of the said coefficient but depends also on the extremely variable and sometimes sudden reduction of the hemoglobin that remains intact.

H. R. WOLCOTT.

SUDDEN OR UNEXPECTED DEATH FROM ILLUMINATING GAS. M. PRATI, Arch. di antrop. crim. **47**:1007, 1927.

Sudden or unexpected death from the inhalation of large quantities of illuminating gas is usually interpreted as due to the sudden suppression of the flow of oxygen to the bulbar centers. Not satisfied with this explanation, Prati carried on a series of experiments with rabbits and reports the following results: 1. The passage of illuminating gas through the isolated upper air tracts of the rabbit causes rapid death through the immediate stopping of respiration and the heart's action. 2. Death is prevented by the cocainization of the nasal mucosa, severing

of the branches of the vagus nerve, and by the atropinization of the experimental animal, which is interpreted as due to a respiratory inhibition reflex. 3. Death by a reflex mechanism is not observed if the illuminating gas is introduced into the lungs without coming in contact with the mucosa of the primary air passages. If death does ensue, it is only after a time, when a sufficient amount of gas has been absorbed, and is attended with the gradual and slow weakening of the vital functions through a mechanism that is evidently of a toxic nature. 4. If death occurs through an inhibition reflex, it is not due to carbon monoxide but to some other component of illuminating gas — in all probability, the hydrocarbons.

H. R. Wolcott.

Blood Groups and Their Practical Importance in Questions of Parentage. Hermann Merkel, Arch. f. Gynäk. **131**:188, 1927.

A review of the work on inheritance of blood groups includes special reference to Bernstein's hypothesis of the three multiple allelomorphs which, besides supporting the older claim that either agglutinogen A or B if present in a child must be present in at least one parent, also eliminates a person of group AB from parental relationship with a child O, and likewise a person of group O from being the parent of a child AB. If the mother and child belong to the same group, investigation of the blood group of an alleged father is inconsequential, for all groups are possible except for children of group O or AB as noted. In seven of seventy cases considered, the man accused of being the father was eliminated as of an impossible group. In each of five cases in which two men were considered, one was eliminated by an impossible group and the other found "possible." In forty-seven of seventy-eight cases the mother and child were in the same group: nineteen times they were in group O in which instance a father of group AB only could be eliminated; in twenty-five they were in group A, and in three they were in group B. In no cases were a mother and child both found in group AB. Of forty-three cases in which the blood group of the accused man was determined, twenty-one cases involved a decision between two men, and in fifteen of these cases both men belonged to "possible" groups; so no practical aid from the study of the blood grouping was forthcoming. The necessity for reliable technic and unassailable results for medicolegal application is emphasized.

Ethel B. Perry.

Experiences with Arsenic Poisoning. A. M. Marx, Deutsche Ztschr. f. d. ges. gerichtl. Med. **11**:36, 1927.

There were twenty-two cases of poisoning with arsenic in which the patients were treated at the Institute for Legal Medicine in Prague during the years from 1919 to 1923. Fifty-five persons were made ill and of these thirty-two died. All were cases of acute poisonings. Postmortem examinations were made of six bodies in the Institute, and organs from the twenty-six bodies examined in outlying districts were sent to Prague. Fifteen deaths occurred among thirty-eight persons poisoned in seven separate affairs of one sort or another. It was decided that 6 of the deaths were suicidal, 4 murder, 1 accidental, 1 resulted from neoarsphenamine, 2 from attempts to bring on abortion and in 8, the evidence was insufficient to determine just how poisoning occurred.

In addition to the usual abdominal pains, vomiting, dry or burning mouth and throat, and diarrhea, two patients experienced sudden blindness and four had a bitter taste which one compared to that of horse radish. Emphasis is given to the difficulties attending the clinical recognition of arsenic poisoning, for which meat poisoning, gastro-enteritis, vomiting of pregnancy and impending abortion are frequently diagnosed. In one patient, anuria was a conspicuous symptom, and mercury poisoning was suspected.

The gross appearance of the kidneys may also suggest mercuric poisoning. Acute inflammation of the stomach and bowel with fatty changes of the liver and kidneys were usually found after death, with sometimes hemorrhages in the

serous covering of the lungs and heart. The fatty change of the liver may be like that caused by phosphorus. Subendocardial hemorrhages are not emphasized by Marx. Granules of white or yellowish material subsequently demonstrated to be arsenic were found in the small bowel three times, in the colon once.

No evidence was obtained for the rather prevalent notion that arsenic poisoning delays postmortem decomposition. Arsenic poisoning was determined only by chemical examinations, although it was regarded as highly probable when during the course of seven of the postmortem examinations, particles were found in the stomach which at the time were thought, and subsequently proved, to be arsenic.

E. R. Le Count.

Comparative Refrangibility of the Blood of the Two Sides of the Heart as a Test for Death from Drowning. Georg Canuto, Deutsche Ztschr. f. d. ges. gerichtl. Med. **11**:72, 1927.

A great many tests for death by drowning have been studied and used depending on the absorption in the lungs of water into the blood, its transport into the left auricle and ventricle and the resulting differences of the blood in the right and left chambers of the heart. Comparison of the blood of the two sides as to the amount of hemolysis, changes of color index, percentage of solids, number of red cells, swelling of the red cells, electrical conductivity and examinations for chemical substances foreign to normal blood have been made.

In dogs experimentally drowned, the greater dilution of the blood found in the left ventricle has been easily demonstrated by refractometry (Szulislawska and Tobiczyk: *Deutsche Arch. f. d. ges. gerichtl. Med.*, 1927, vol. 9, p. 13). Canuto believes this is more reliable than tests such as freezing point and electrical conductivity measurements which depend on the amount of dissociable salts, substances more easily diffused into and through the walls of the heart than the colloids responsible for variations in refraction.

By measuring its refraction index, he found the blood from the cavities of the left ventricle thinner than in the right in thirteen of sixteen bodies of persons drowned, bodies examined at the Institute of Legal Medicine in Turin, Italy, during the years from 1923 to 1926. In the other three bodies, postmortem decomposition had made this test impractical.

E. R. Le Count.

An Extensive Ice-Cream Poisoning. H. Braun and F. Mündel, Klin. Wchnschr. **6**:1286, 1927.

In Offenbach on the Main, eighty-nine persons partook of ice cream in August, 1926, and eighty-seven became acutely ill. The average duration of the fever was slightly less than two days. No deaths are reported. The bacilli isolated from the ice cream, and from the blood, stools and urine of the patients were identified as *B. suipestifer*, an organism not generally regarded as pathogenic for man. It is believed that the great number consumed with the ice cream was a factor in causing illness. Some patients had herpes, roseolae and an enlarged spleen.

E. R. Le Count.

Technical

The Kahn Test in Spinal Fluid. P. G. Hull, L. Fry and C. Garwood, Am. J. Syph. **12**:104, 1928.

The Kahn test "has a high degree of specificity in eliminating the possibility of cerebrospinal syphilis."

The Laboratory Diagnosis of Syphilis. I. Davidsohn, Am. J. Syph. **12**:122, 1928.

The Kolmer complement-fixation test for syphilis is the method of choice. In this country, it is practically specific for syphilis, while in tropical regions, it is

also positive in cases of frambesia tropica. The Kolmer test when properly conducted is free from nonspecific positives. Weakly positive complement-fixation tests obtained with the Kolmer method indicate the presence of syphilis and should be taken as seriously as strongly positive reactions. Repetition of tests on doubtful and negative cases is advocated. Examination in the dark-field is the method of choice in early stages of the disease, the complement-fixation test occupying second place. The cell count, colloidal tests and the globulin estimation are of help in diagnosing syphilis in the spinal fluid only in conjunction with the complement-fixation test. The Kahn precipitation test is of help as an adjunct of the complement-fixation test, but cannot replace the latter.

AUTHOR'S SUMMARY.

THE KAFKA PARAFFIN REACTION IN THE SPINAL FLUID. LOUIS J. KARNOSH and A. J. RADEMAEKERS, Arch. Neurol. & Psychiat. **19**:125, 1928.

The authors modified the reading of the Kafka curve to make simple a comparison with the gum mastic test and recognized five instead of six degrees of precipitation. Fluids were examined in cases of general paralysis, tabes, syphilis of the central nervous system, meningitis, extraneural syphilis, various organic neurologic conditions and in the psychoses. They recommend the Kafka paraffin colloidal test on the spinal fluid as a simple and reliable procedure. The technic is somewhat more difficult than that of the gum mastic test because of the temperature requirements.

T. T. STONE.

COLLOIDAL GOLD REACTION WITH SPINAL FLUIDS CONTAINING BLOOD. HENRY G. MEHRTENS, HARRY A. WYCKOFF and REVA M. DAVIS, Arch. Neurol. & Psychiat. **19**:296, 1928.

Spinal fluids which have become mixed with blood, but from which all cells are removed by centrifugalization before hemolysis has taken place, give the same type of colloidal gold curve as the same fluid without the admixture of blood.

INFLUENCE OF MALARIAL TREATMENT ON THE SPINAL FLUID IN GENERAL PARALYSIS. H. A. BUNKER, JR., Arch. Neurol. & Psychiat. **19**:478, 1928.

Observations on the spinal fluid appear to be of prognostic significance only in a negative sense. A satisfactory response is not necessarily of favorable import; but the few cases in which reduction in the cell count does not take place with more or less promptitude or in which pleocytosis reappears, and those in which the total protein in the spinal fluid remains at or returns to a level in excess of 100 milligrams per hundred cubic centimeters, seem to offer definite evidence of a minimum therapeutic result. The behavior of the Wassermann reaction in the spinal fluid does not seem to possess a decisive significance; but whether the cases with a more negative reaction will compare favorably with those with a less negative one regarding the ultimate duration of the therapeutic result achieved is a question to be answered in the future.

AUTHOR'S SUMMARY.

ON THE PATHOLOGY AND LABORATORY DIAGNOSIS OF PARESIS. FREDERICK PROESCHER and ALBERT ARKUSH, J. Nerv. & Ment. Dis. **67**:21, 1928.

The authors speak of a method to determine the diagnosis of general paralysis during life and post mortem by the use of a chemical to precipitate iron. The former they claim is performed by centrifugalizing 10 cc. of spinal fluid, and to the sediment is added 5 cc. of an alcoholic ammonium hydroxide sulphide solution. This is then centrifugalized and a few drops of the sediment examined on slides under the cover glass. The iron-containing cell is found only in the adventitial cells, which are large, irregular and refractile. These cells may be seen with a high dry objective. The method at postmortem examination consists of taking small pieces of unfixed brain from the cortex and washing with

physiologic sodium chloride solution or tap water and immersing for from fifteen minutes to twelve hours in concentrated ammonium sulphide. Usually after from twelve to twenty minutes the entire cortex shows a diffuse grayish-green coloration especially in the lower strata. This coloration is due to a diffuse iron reaction characteristic for the cortex of any normal adult brain. The characteristic feature in cases of paralysis is the presence of small black points and striations in the cortical gray matter. These points and striations are blood vessels made visible by the ammonium sulphide.

For microscopic examination small pieces of brain containing black points are removed by means of a glass needle or porcelain spatula and crushed between slides and examined in glycerin. Under the low power lens small and large blood vessels can be seen surrounded at a short or long distance with deep black or light gray irregular granules. Under a high magnification lens, these granules are seen to be in the cells of the vessel walls. These cells belong to the so-called third element or Hortega cells (microglia of some authors). The iron reaction has been found in material several days old. Alcohol fixation usually will not interfere with iron reaction, but solution of formaldehyde will.

T. T. STONE.

Society Transactions

AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

Ann Arbor, Michigan, April 12, 13, 14, 1928

DAVID MARINE, *President, in the Chair*

AFEBRILE POSTSCARLATINAL NEPHRITIS. CHARLES W. DUVAL, New Orleans.

Both the living culture of *Streptococcus scarlatinae* and its in vivo prepared toxin induce an acute glomerular nephritis. The lesion in the kidney occurs during the infection and may also be induced in the recovered animal several weeks later by injections of the in vivo prepared lysate, and also by large amounts of living culture, without causing reinfection. There is abundant experimental proof that the streptococcus is responsible for the acute glomerular nephritis during the infection and for the so-called afebrile nephritic period which occurs weeks later. From the results of the author's experiments, it appears that scarlatinal infection in the dog establishes a lytic rather than an antitoxic immunity. If this is true for the human infection, it is logical to suppose that the persistence of hemolytic streptococcal foci in the respiratory tract, etc., would be the source of an intermittent supply of toxic product to the system. A comparative study of the scarlatinal nephritis in the dog experimentally induced by the filtered in vivo prepared toxin shows a complete analogy with the afebrile postscarlatinal nephritis of man.

THE EFFECT OF AN AD LUXUS MEAT DIET ON THE KIDNEY OF THE WHITE RAT. ROBERT A. MOORE, Columbus, Ohio. (Introduced by Howard T. Karsner.)

Forty-three animals were studied in all; twenty-three were experimental animals and were fed on a diet containing 36 per cent of protein, of which 7 per cent was contributed by lean beef. The experimental and control rats were of the same age and in many cases were litter mates. The feeding of meat was continued for from 300 to 450 days.

Comparison of the weights of the organs revealed that the kidneys of the experimental animals on the average are 14 per cent greater in size than those of the control, which is two and one-half times the probable error. Determinations of blood pressure comparing the two groups were negative.

Histologic examination of the kidneys revealed that 10 per cent of the control groups showed changes of a minor nature, while 76 per cent of the experimental group showed changes which in all cases exceeded those seen in the controls. These changes in the order of their frequency are dilatation of the tubules with hyaline casts, cellular infiltration about the distal convoluted tubules, thickening of the glomerular capsule and endarteritis.

THE TOXICITY OF MERBAPHEN AND ITS ACTION ON THE KIDNEY OF THE RABBIT. B. I. JOHNSTONE and H. M. KEITH, Detroit. (Introduced by F. W. Hartman.)

The toxicity of merbaphen was studied by injecting it intravenously into the rabbit and examining the gross and microscopic lesions produced in the kidney. Thirty-two animals were used. Doses of 0.7 cc. per kilogram killed the rabbit within three minutes. Doses of 0.168 cc. per kilogram and over were lethal. If lethal doses were given but death was not immediate, the length of life after treatment varied directly with the size of the dose. The maximum single tolerated dose was estimated as 0.09 cc. per kilogram, or about 3 mg. of pure mercury.

Repeated doses of 0.05 cc. per kilogram were consistently toxic. In a number of instances, considerably smaller repeated doses produced death. Rabbits given a single fairly large nonlethal dose and then allowed to recover were able to withstand much larger repeated doses than those not receiving such an initial dose. Rabbits given single doses of 0.1 cc. per kilogram and over showed damage to the kidney as early as one hour after injection, and these lesions became progressively more severe in direct proportion to the size of the dose and the time elapsed following injection. The pathologic lesions produced in the kidney by toxic doses were studied in detail. These proved to be similar to those produced by the other mercury compounds in common use. They consisted of a tubular degeneration, with regeneration after the third day and deposition of calcium as early as the fourth day after injection.

THE LOCAL MICROSCOPIC CHANGES FOLLOWING INTRAMUSCULAR ADMINISTRATION OF ANTISYPHILITIC DRUGS. O. M. GRUHZIT, Detroit. (Introduced by CARL V. WELLER.)

Intramuscular administration of arsphenamine, neoarsphenamine, silver arsphenamine and sulpharsphenamine in doses of 0.04 to 0.045 Gm. causes severe microscopic changes at the site of injection. All tissues in contact with the inoculum become necrosed. The blood vessels are thrombosed and the nerve trunks destroyed. The lesion essentially represents a coagulation necrosis which inside of seven days becomes encapsulated. The absorption of the necrotic material is slow. It undergoes liquefaction and cystic degeneration with gradual absorption and replacement by connective tissue. At the end of eight weeks, the lesion has shown a minor degree of healing. Sulpharsphenamine causes just as great injury as is found when neoarsphenamine is used. Healing is more rapid in an active muscle of the thigh than in a passive lumbar muscle.

Pathologic changes caused by the administration of mercurial preparations intramuscularly are similar in nature to the injury caused by the injection of arsphenamine, except that the necrotic tissues possess leukocytic chemotaxis and consequently the liquefaction necrosis is more rapid. Mercury attached to the —SH group appears less injurious to the tissues; otherwise, mercury salts, whether soluble or insoluble, appear equally destructive to the tissues.

Bismuth preparations of insoluble or soluble salts induce injury to tissues according to the degree of the corrosiveness of the preparation. The injury from oil suspensions is less than from water solutions, except in the case of bismuth thioglycollate, which causes the least injury of all types of bismuth compounds studied. With the exception of bismuth thioglycollate, a degree of necrosis is produced which is followed by caseation necrosis, deposit of lime salts, encapsulation of the connective tissue and finally formation of scar tissue. Bismuth thioglycollate constitutes an exception. A minimal degree of injury follows the injection of this preparation, and inside of three weeks the lesion is completely fibrosed and becomes a quiescent scar.

STUDIES OF BLOOD AND BLOOD SERUM: SPECTROPHOTOMETRIC CURVES OF SERUM FROM PATIENTS WITH A DEFINITE CLINICAL HISTORY. W. H. SCHULTZ, Baltimore.

Blood samples were collected from patients in the University Hospital, Baltimore, by Dr. P. R. Rockwood, who also read the icterus index of each sample and made van den Bergh tests on the serums studied. The writer is responsible for the chemical and physical studies represented by the spectrophotometric curves.

Lantern slides were made from the original curves plotted in groups for comparative study.

SLIDE I.—Spectrophotometric curves of chemically pure crystals dissolved in solvents of known p_H values.

1. Oxyhemoglobin dissolved in water.
2. Bilirubin dissolved in alcohol.
3. Biliverdin dissolved in alcohol.

SLIDE II *a*.—Absorption curves of serums from patients with catarrhal jaundice. Van den Bergh reactions prompt, direct and quantitatively ranging from "too little pigment to determine" to as high as 9.4 mg. The icterus index was as high as 50.

SLIDE III *a*.—Absorption curves of serum from patients with cholecystitis. The van den Bergh quantitative tests ranged from 2.5 to 8.6 mg. of bilirubin. The arbitrary icterus index ranged from too dark to read to one of 26.

b.—Absorption curves of the alcohol-acetone extracts of serums (*a*) compared with cases showing pure bilirubin.

SLIDE IV *a*.—Absorption curves of serums from patients with acquired hemolytic icterus. The van den Bergh test varied in type, indirect or delayed direct. The quantitative test ranged from 2.8 to 6 mg., and the icterus index ranged from 23 to 33.

SLIDE V.—Absorption curves from serums of patients with carcinoma.

22 *a*. Of the head of the pancreas — van den Bergh, direct, prompt, quantitative 10.2 mg. Icterus index, 160.

47 a. Of the gallbladder — van den Bergh test, direct, prompt, quantitative 14.3. Icterus index, 138. Alcohol-acetone extracts of serums 22 *a* and 47 *a* both yielded absorption curves resembling that of pure bilirubin, but 47 *a* seemed contaminated with biliverdin.

SLIDE VI.—Absorption curves of serums from patients showing secondary anemia. The van den Bergh test varied, being indirect with bilirubin present in such small amounts as to render reading impossible. In others, the van den Bergh test was biphasic, the serum too brown for the icterus index to be read. The extracts were difficult to handle and the types of absorption curve varied with what seemed to be a mixture with biliverdin, bilirubin and in some cases an unknown substance that caused the absorption curve to differ from that of a simple mixture of bilirubin and biliverdin.

SPIROCHETOSIS OF THE CENTRAL NERVOUS SYSTEM IN GENERAL PARALYSIS. ROBERT R. DIETERLE, Ann Arbor. (Introduced by A. S. Warthin.)

The demonstration consisted of further investigations in a case of juvenile general paralysis reported by Dr. Dieterle (*Am. J. Psychiat.* **7**:547, 1928) as representative of Jahnel's type of perivascular spirochetosis in association with the "bee-swarm" or colony formations. Lantern slides and microscopic sections of the cerebral cortex, basal ganglions and cerebellum with total sections of the hemisphere of this brain were shown to illustrate the unusual intensity of the spirochetosis with reference to histologic and topographic locations.

Besides the aspect of intensity and localization in relation to possible avenues of invasion and dissemination, it was shown that the secondary degenerative processes within the basal ganglions point toward an older spirochetosis and possibly a primary invasion of these regions.

The investigations were carried out with modifications of Jahnel's uranoformol method for total blocks and with the author's method for impregnation of single microscopic sections (*Arch. Neurol. & Psychiat.* **18**:73 [July] 1927).

In addition, negative symptoms were reported in three patients with general paralysis dying during the course of malarial therapy. The negative results were regarded so with reserve, due to the somewhat limited amount of material investigated to date.

THE INTERCONVERTIBILITY OF R AND S BACTERIAL TYPES OF BACILLUS PARATYPHOSUS B. M. H. SOULE, Ann Arbor.

Serial cultivation of the S and R types of *B. paratyphosus* B (209 S, 209 R, 210 S, 210 R, Jordan strains) in the presence of homologous immune serums elicited the dissociation of both forms. R forms appeared in strain 209 S after five serial transplants in homologous serum broth and in the 210 S strain after two such

transfers. S types appeared in strain 209 R after the seventh transfer in homologous serum broth and in strain 210 R after the sixth transfer. The R and S forms produced in this manner had all of the characteristics of the original R and S cultures. Practically no dissociation occurred in the S types when grown in the presence of R serum. S forms appeared in the R strains grown in the presence of the nonhomologous serum, but the number never became large with continued serial transplanting. The most favorable concentration of serum for inciting dissociation was 10 per cent. Dissociation of the strains was not observed when serially cultured in broth containing like quantities of normal serum or in plain infusion broth of p_H 7.4 and 7.8. Broth containing ox bile or pancreatin was an excellent medium for dissociating these forms if the reaction was about p_H 6.5. The S type was more strongly antigenic. The immune serums agglutinated their homologous organisms but not the heterologous forms. The lethal dose of the S form for guinea-pigs was 500 million. The R form was nonvirulent. Guinea-pigs immunized by the R form were resistant to ten lethal doses of the S form. Rabbits immunized to the R and S form were injected intravenously with 1 billion living homologous germs. At twelve hour intervals, 5 cc. of blood was drawn and cultures were made. After thirty-six hours, the organism had usually disappeared from the blood stream. Dissociation did not take place in the animal body under these conditions.

STUDIES ON BLOOD CALCIUM OF NORMAL AND PARATHYROIDECTOMIZED ALBINO RATS. W. R. TWEEDY and S. B. CHANDLER, Chicago. (Introduced by F. C. Koch.)

The blood plasma calcium of normal albino rats varies from 9.25 to 12.5 mg. per hundred cubic centimeters. Unilateral parathyroidectomy does not appreciably change this value. After bilateral parathyroidectomy, the blood plasma calcium usually drops from 3 to 4 mg. within from twenty-four to forty-eight hours. Observations extending over as long as seven months indicate that the plasma calcium of the individual parathyroidectomized rat usually varies between 5 and 8 mg. per hundred cubic centimeters. Values of blood plasma calcium obtained on the administration of standardized parathyroid extract indicate that the completely parathyroidectomized rat is two or three times more reactive than the normal rat. According to Collip's (*J. Biol. Chem.* **54**:494, 1925) observations on dogs, there is no appreciable difference in response of normal and parathyroidectomized dogs to parathyroid extract.

THE POTASSIUM-CALCIUM RATIO OF THE LYMPH OF DOGS DURING BACTERIAL SHOCK. W. F. PETERSEN, ERNST F. MÜLLER and GEORGE MILLES, Chicago.

Following incanulation of the thoracic duct under local anesthesia, dogs were injected intravenously with a continuous suspension of *B. coli* (1 slant to 500 cc. Ringer's solution) and the clinical reaction studied (temperature, rectal and muscle, the leukocyte count, the urine, etc.) as well as an analysis made of the lymph (volume, potassium, calcium, nonprotein nitrogen, protein, enzymes, carbon dioxide combining power, presence of bacteria, etc.). The periodic fluctuations in the mineral balance, in the protein concentration, the lymph volume, the leukocyte count, etc., afford striking evidence of the alternating periods of stimulation and recovery in the splanchnic area. Evidence is presented that the chill is not associated with the production of heat in the muscles. Bacteria enter the lymph stream only at a time of severe injury and then only for a short time. The period of greatest injury is associated with a low potassium-calcium ratio; a premortal recovery occurs, due probably to liberation of potassium from red blood corpuscles.

THE INFLUENCE OF DIET ON THE PRODUCTION OF ASCITES. J. L. BOLLMAN, Rochester, Minn.

Definite ascites has rarely been observed in experimental animals. In a large number of dogs, maintained from four to six months after ligation of the com-

mon bile duct on a diet consisting essentially of carbohydrate, milk, bread and syrup, evidence of ascites was ordinarily not observed. It has been found that in most of these animals in which obstructive jaundice has existed for three or more months definite ascites will develop after a few days of feeding of meat. More than 2 liters of ascitic fluid have accumulated in dogs weighing from 5 to 7 Kg. after a few days on this diet. The ascitic fluid is clear, pale yellow and, except for the small amount of protein, is essentially of the same composition as serum. Resumption of the carbohydrate diet has, in most instances, been accompanied by diminution and disappearance of the ascites. Merbaphen has been effective in the removal of the ascitic fluid, but it has recurred in a few days with continuance of feeding of meat. The addition of meat extract (Leibig's) to the carbohydrate diet seems even more effective in the production of ascites than the feeding of meat. Within six hours after the meat extract was given (50 Gm. to a dog weighing 6 Kg.), approximately 1,500 cc. of ascitic fluid was present in a dog in which ascites had not previously been present. The animals are allowed free access to water, and experiments are now under way to determine what proportion of the ascitic fluid may be accounted for by the water taken by mouth with and subsequent to the experimental feedings. Similar experiments in feeding have been carried out with dogs the livers of which are extensively impaired (animals with cirrhosis following repeated administration of carbon-tetrachloride and partial hepatectomy), but formation of ascites has not been demonstrated.

PASSAGE OF DEXTROSE FROM THE PERITONEAL CAVITY IN PERITONITIS. BERNHARD STEINBERG (Introduced by H. T. Karsner) and ELEANOR ROBB, Toledo.

Dextrose introduced intraperitoneally in dogs was found to pass, apparently independently, by the lymphatics and the blood vessels into the blood and lymph. The greater part of the dextrose was found in blood within fifteen minutes subsequent to the injection of the dextrose intraperitoneally. The peak of dextrose content in the blood was found to be from 60 to 90 minutes after the dextrose was injected into the peritoneal cavity. The blood sugar returned to normal from four to seven hours later. The maximum amount of dextrose in milligrams per hundred cubic centimeters of blood following the intraperitoneal injection of 200 cc. of 18 per cent dextrose varied from 200 to 357. Dogs that were actively immunized by intraperitoneal injections of colon bacilli did not show appreciable changes in the passage of dextrose from the peritoneal cavity. Dogs in which peritonitis was produced by injection of fecal material intraperitoneally showed variations from the normal. In early peritonitis (eight hours) with distention and congestion of blood vessels, there was a moderate diminution in the amount of dextrose passing from the peritoneal cavity. The peak was reached in an hour. In a moderately late peritoneal infection (thirty hours) with a hemorrhagic fibrinous peritonitis, there was a marked diminution in the passage of dextrose from the peritoneal cavity. The peak was reached in an hour. The dextrose content of the blood returned to its normal level in one and one-half hours.

STUDY OF THE ACID-BASE EQUILIBRIUM IN RELATION TO OCCURRENCE OF EPILEPTIC CONVULSIONS. IRVINE MCQUARRIE and H. M. KEITH, Rochester, New York.

Factors concerned in the regulation of the acid-base equilibrium were studied in a group of epileptic children under a variety of experimental conditions. Data were obtained at intervals before and after seizures which were induced by administration of carbohydrate or sodium bicarbonate to subjects with severe epilepsy after they had been brought under control by means of the ketogenic diet or fasting. It was found impossible to induce convulsions in persons with mild epilepsy during the free intervals between regular attacks by giving carbohydrate,

by forced breathing or by administering sufficient alkali almost to double the plasma carbon dioxide content and to raise the blood p_H by as much as 0.3 p_H. However, in the patients with the more severe cases, who had frequent seizures when not under treatment, these procedures resulted regularly in the recurrence of attacks. Following the intensive administration of dextrose over a period of twelve hours, it was observed that the plasma p_H and carbon dioxide rose steadily to levels well above normal before convulsions occurred. Under these conditions the pre-existing ketosis was found to disappear several hours before the recurrence of seizures and before the blood p_H and carbon dioxide reached their maximum levels. When sodium bicarbonate was given, attacks recurred within the course of a few hours, preceded by a marked increase in the acetone bodies of the blood and urine and in the p_H and carbon dioxide of the plasma. While there is therefore strong evidence of a disturbance in the acid-base balance preceding epileptic seizures, the conclusion cannot be drawn that this is the main factor in their causation.

CATAPHORETIC MIGRATION OF BLOOD CELLS IN SOLUTIONS AND GELS WITH REFERENCE TO SURFACE COMPOSITION AND LEUKOCYTE EMIGRATION. H. A. ABRAMSON, New York. (Introduced by A. M. Pappenheimer.)

The cataphoretic velocity of red cells in serum (horse) is about 1.0 micron per second per volt per centimeter. Polymorphonuclear leukocytes migrate at about half this speed (Freundlich and Abramson: *Ztschr. f. phys. Chem.* **128**:25, 1927. Abramson: *J. Exper. Med.* **46**:987, 1927). Small lymphocytes migrate 20 or 30 per cent faster than leukocytes. Similar values are obtained for oxalated plasma. The cataphoretic velocity is proportional to the applied electromotive force. As neither the shape nor the size of the particle causes significant variations in cataphoretic velocity, the variations in cataphoretic velocity found must be due to a difference in surface composition. The nature of this difference was determined by studying the cataphoretic velocity of quartz particles in protein solutions and gels. Quartz particles surround themselves with an adsorbed film of protein in comparatively dilute protein solutions, thus having the same cataphoretic velocity as the protein micelles themselves. (Abramson: *J. Am. Chem. Soc.* **50**:390, 1928). In serum, quartz particles and polymorphonuclear leukocytes have an equal cataphoretic velocity. It may be concluded from this that both quartz and polymorphonuclear leukocytes probably have similar adsorbed protein films. Red cells, on the other hand, perhaps because of their lipoid surface, have a cataphoretic velocity which speaks against a similarly adsorbed film of serum-protein. The same is true to a lesser degree for small lymphocytes. This surface difference is strikingly demonstrated by the cataphoretic velocity of quartz particles, red cells and leukocytes in certain soft gelatin-serum gels. The quartz particles and leukocytes, as in serum, migrate in such gels with practically the same cataphoretic velocity as the protein micelles of the medium. The red cells, however, keep their property of independent migration. They migrate through the gel about twice as fast as the leukocytes. There is relatively little change in the absolute cataphoretic velocity of all the particles, although a gel is present. The presence of such a soft gel structure as found in gelatin gels has little influence on migration when the force producing migration is electrical. Gels that have been studied have been stiff enough to prevent the cells from settling out. The experiments outlined are suggestive that electromotive force between the zone of injury and relatively normal tissue (calculated as volts per centimeter) are of a sufficient order of magnitude to produce the migration of a leukocyte through the gel wall of the capillary and to the point of injury cataphoretically. Blood platelets and polymorphonuclear leukocytes have the same cataphoretic velocity. This suggests that the adsorbing surfaces of these cells are the same and hence that they both arise from the same type of marrow cell (Abramson: *J. Exper. Med.*, to be published).

THE INFLUENCE OF MYRTILLIN ON THE CARBOHYDRATE METABOLISM OF TISSUES. RICHARD J. WAGNER, Morristown, N. J. (Introduced by F. M. Allen.)

In in vivo experiments, myrtillin affects the oxygen consumption of man and dog after carbohydrate intake in such a manner that less oxygen is required and the height of the oxygen requirement is reached at an earlier stage of digestion. Determinations on several persons with and without myrtillin show that the respiratory quotient rises more quickly under the influence of myrtillin and goes above 1 in thirty minutes. In a short time, it drops again to the fasting level. The amount of carbon dioxide produced is unchanged. Myrtillin does not have any effect on animals such as goats, rabbits and rats, which have enough of the natural sources of myrtillin in their food.

Experiments in vitro were performed with hashed muscle and liver of dogs and rabbits, a modification of Warburg's respiration apparatus (*Biochem. Ztschr.* **142**:317, 1923) being employed. The 250 cc. container was filled with 100 cc. of Locke's solution containing 200 mg. per hundred cubic centimeters of dextrose. The liquid was saturated with oxygen, after which 25 Gm. of the finely ground liver or muscle was added. Consumption of oxygen, carbon dioxide production and sugar content were estimated after the container was shaken for three hours in the water bath at 37 C. It was found that myrtillin diminishes the oxygen consumption of the muscle of normal dogs between 24 and 40 per cent, increases the oxygen production about 10 per cent and the sugar consumption, from 26 to 35 per cent, as compared to controls. The same experiments with muscle hash of rabbits do not show a difference with or without myrtillin. The hashed liver of normal dogs showed the same effects of myrtillin in diminishing the oxygen consumption and increasing the sugar consumption about 40 per cent, but the oxygen production remained unchanged. Myrtillin does not have an effect on the carbohydrate metabolism of rabbit liver. The liver of totally depancreatized dogs gives the same results as the liver of normal dogs. The combination of myrtillin with insulin does not show other effects than myrtillin alone.

In all of the experiments with myrtillin, there are two different minimums to distinguish. At a certain minimum, the oxygen diminishing effect occurs. With a little higher dose of myrtillin, the increase of sugar consumption sets in. No higher dose than the certain minimum produces any further effect. For different preparations of myrtillin, different minimums are required. It is suggested, therefore, to use the in vitro tests for standardizing purposes.

In conclusion, myrtillin develops the same oxygen saving effect in experiments with the surviving tissue as in vivo. But apparently it has only a small, if any, effect on the burning process and, therefore, on the carbon dioxide production. It has a marked effect, however, on the assimilation of administered dextrose. It enables the cells of the surviving tissue to consume between 24 and 40 per cent more of the added sugar than the controls.

FURTHER OBSERVATIONS ON THE PRODUCTION OF LESIONS IN THE HEART BY DEEP ROENTGEN-RAY. F. W. HARTMAN, Detroit.

In continuation of the work reported before this society last year, an attempt has been made to localize the area of radiation more accurately when the rays are projected through the right and left side, also through an incision in the wall of the chest. Explanation for the electrocardiographic changes has been sought in the study of nodal tissue, conduction bundle and coronary vessels as well as in the myocardium.

THE EFFECTS OF IRRADIATION ON THE HEART. A. S. WARTHIN and E. A. POHLE, Ann Arbor.

In an earlier study (*J. A. M. A.* **89**:1825, 1927) series of rats and rabbits were exposed to roentgen rays of short wave length with a surface dose equaling one human erythema dose. Clinical symptoms representing signs of roentgen-ray injury to the heart could not be noted and there were no gross pathologic changes.

Microscopically, in one rabbit and in two rats only were there changes which could be interpreted as having been due to the irradiation. The present work continued the previous study and is concerned with the pathologic changes produced by a single exposure equal to three human erythema doses. The microscopic study of animals so exposed shows much more marked pathologic changes in the myocardium consisting of fatty degenerative infiltration and Zenker's necrosis. In some of the hearts, these changes were comparable to the severe parenchymatous changes seen in certain cases of human diphtheria. From this work it must be concluded that intensive irradiation is capable of producing serious damage to the heart muscle.

A Study of the Intradermal and Subcutaneous Injection of Calcium Chloride in the Presence of Roentgen-Ray and a Possible Relationship to Malignant Disease. A Preliminary Report. F. A. Hecker, Ottumwa, Iowa. (Introduced by M. T. Burrows.)

Rats were given intradermal and subcutaneous injections of from 0.5 to 1.5 cc. of a 2 to 10 per cent solution of calcium chloride. From eighteen to twenty-four hours after the calcium chloride was injected, the rats were irradiated at 130,000 volts, 5 milliamperes, without screens, at 12 inches. The time of the irradiation varied from five to thirty minutes. The calcium plus the roentgen-ray ulcer and the calcium ulcer were of similar appearance, while the roentgen-ray ulcer did not resemble the calcium roentgen-ray or calcium ulcer. It is believed that the calcium injected is excessive and that it depletes the vitamin A in the area into which it has been injected to such a low level that the vitamin A is unable to activate the calcium.

Changes in Blood Sugar in Peptone Shock in the Dog. W. W. Brandes and J. P. Simonds, Chicago.

Hypoglycemia occurs shortly after the intravenous injection of peptone, that is, during the period when blood pressure is low and the liver markedly congested. As the blood pressure rises and the liver relaxes, a marked hyperglycemia is found in blood taken from the femoral vein. Samples of blood taken from the hepatic veins show a marked increase in blood sugar at the time when the liver is most congested, that is, at the time when blood from the femoral vein shows a decrease in sugar. An explanation of these observations lies, perhaps, in the fact that in peptone shock there is an interference with the free flow of blood from the liver, with congestion and stasis, giving rise to increased glycogenolysis in the liver. During the height of the shock so little blood leaves the liver that, although its sugar content is high, there is not enough entering the general circulation to maintain the normal sugar level, and hypoglycemia results. As the obstruction is overcome and the liver relaxes, the blood from the liver with its high sugar content enters the general circulation in increasing amount, giving rise to hyperglycemia.

The Effect of Peptone on the Hepatic Veins in the Dog. J. P. Simonds and W. W. Brandes, Chicago.

By means of a specially constructed oncometer and a manometer connected with a cylinder fitted with a syphon, alterations in the outflow from and the volume of a perfused dog liver were simultaneously and mechanically recorded. The perfusion fluid consisted of well oxygenated, diluted, defibrinated blood from the same animal in which the liver was being perfused. With this mechanical device it was shown (1) that when peptone is injected with the perfusion fluid entering the liver by the portal vein there is a decrease in outflow and an increase in the volume of the liver, and (2) that when peptone is injected with the perfusion fluid entering by way of the hepatic vein there is a decrease both in outflow from and volume of the liver. Uniform results were obtained with the livers of eight dogs. The conclusion seems warranted that peptone causes a constriction of the hepatic veins in the dog.

BILE SALT METABOLISM—INFLUENCE OF TRYPTOPHAN AND ISATIN IN THE DOG WITH A BILE FISTULA. H. P. SMITH and G. H. WHIPPLE, Rochester, New York.

The total output of bile salt in dogs with bile fistulas varies markedly with the diet. A large output results when the animals are maintained on a pure meat diet. Much less is obtained on a special mixed diet. Addition to this mixed diet of cholesterin in the form of egg yolk does not lead to excretion of additional quantities of bile salt as one might expect from the close chemical relationship thought by many to exist between cholesterin and bile acids. In animals on a gelatin diet, little bile salt is excreted. Addition of tyrosine to the diet is without effect, but if the gelatin diet is supplemented with tryptophan or with a closely related compound, isatin, large amounts of bile salt appear in the bile. From these two groups of experiments it would seem that cholesterin is not directly concerned in the formation of bile salts but that tryptophan and isatin do play an important rôle.

OBSERVATIONS ON THE EFFECTS OF SERUMS FROM NORMAL AND ANEMIC PERSONS ON SEEDLING GROWTH. RAPHAEL ISAACS, LOVE BARNETT UPJOHN and FELIX G. GUSTAFSON, Ann Arbor. (Introduced by and paper presented by C. C. Sturgis.)

Studies were made on the effects of serums from patients with various types and in various stages of anemia, on the root growth of lupin seedlings. With the seedlings used in these experiments, serum from patients sick with pernicious anemia did not exert a specific toxic action as compared with that of normal serum or that of patients with secondary anemia. There appeared not to be a correlation between the coefficient of seedling growth and the clinical condition of the patient as measured by the degree of illness, the red blood cell count, the hemoglobin percentage or the amount of blood bilirubin. An appreciable difference was not noted between the coefficient of growth in seedlings with serums from nontreated patients and those with serums from patients treated with liver or liver extract.

AN EXPERIMENTAL INVESTIGATION OF THE BROAD TAPEWORM IN MAN. GEORGE R. LA RUE and T. VERGEER, Ann Arbor. (Introduced by A. S. Warthin.)

The junior author has made examination of many fish from lakes of the lower peninsula of Michigan, from Lakes Ontario, Erie, Huron, Michigan and Superior, and from Portage Lake in the copper country of northern Michigan for the purpose of finding the plerocercoids of *Diphyllobothrium latum*. As a result of his examinations (not yet complete), the fish of the Great Lakes, except those of Lake Superior near the outlet of Portage Lake, appear to be free from infestation with this parasite. Plerocercoids belonging to this genus but not to *D. latum*, were found in the burbot *(Lota maculosa)* and in the lake herring and chubs (*Leucichthys* spp.) from various parts of the Great Lakes. When fed to clean dogs, these plerocercoids developed into an unknown species of *Diphyllobothrium* which is being described elsewhere.

In fish from Portage Lake, Houghton County, Michigan, plerocercoids of *D. latum* were found in the wall-eyed pike, *Stizostedian vitreum*, and the sandpike, *S. canadense-griseum*, in the great northern pike, *Esox lucius*, and in the burbot, *Lota maculosa*. A few plerocercoids were also taken from a wall-eyed pike caught in Lake Superior about twenty miles from Portage Canal. Feeding experiments with clean dogs showed that the plerocercoids from the fish mentioned belong to *D. latum*. By experimental methods, these results confirmed the conclusions of Warthin and others that the broad tapeworm had become established in this region.

In an earlier paper (J. A. M. A. **90**:673 [March 3] 1928), the junior author expressed the belief that the source of infected fish would be found to lie outside

the United States, namely, in Canada. In an examination of forty-seven unfrozen wall-eyed pike from Lake Winnipeg, six plerocercoids were found. Four of these were fed to a clean dog, and eighteen days later four ovigerous broad tapeworms were recovered when the dog was killed. A second clean dog was fed a single plerocercoid. This dog, killed the day this report was read, also yielded a broad tapeworm. Study of this material shows these worms to be *D. latum*.

Further examination of fish from the Great Lakes and from Canadian lakes are in progress to determine the source of those cases of infestation with *D. latum* which occur outside of the two known endemic areas in the United States, viz., the copper country of Michigan and the lake country about Ely, Minnesota. These investigations are being conducted under a grant from the American Medical Association to Professors A. S. Warthin and George R. La Rue.

SOME EFFECTS OF LIGHT ENVIRONMENT. WADE H. BROWN, New York City.

Observations were made on several groups of normal rabbits living in an environment of neon light, in darkness, or in an environment of diffuse, filtered sunlight of varying intensity, for the purpose of determining whether prolonged exposure to such conditions was capable of producing any definite biologic effect. The comparisons made included growth of the animals, growth of hair, blood calcium and inorganic phosphorus, and the organic constitution of the animals as indicated by the weights of organs at the conclusion of the experiments. Parallel observations were made on other animals with respect to their reaction to disease (syphilis). It was found that rabbits living under different environmental conditions showed clearly defined differences in all of these respects.

AN IMPROVED AND SIMPLIFIED METHOD FOR MAKING A STANDARD UNDENATURED TUBERCULIN OF ANY DESIRED STRENGTH AND A CHEMICAL ASSAY FOR THE SAME. FLORENCE B. SEIBERT, Chicago.

IMMUNOLOGIC RELATIONSHIPS OF THE TYPHOID BACILLUS. M. HEIDELBERGER, G. SCHWARTZMAN and D. J. COHN, New York.

THE RATE OF ELIMINATION OF UREA AS A MEASURE OF FUNCTION OF THE KIDNEYS. R. C. LEWIS and INEZ H. MATTISON, Denver. (Introduced by S. R. Benedict.)

Rabbits with nephritis produced by relatively small injections of arsenic, uranium or tartrate showed a significant delay in the elimination of urea as compared to that of normal animals, even when the urea and total nonprotein nitrogen of the blood and the phenolsulphonphthalein excretion were normal. Similar manifestations were obtained in man. As compared to a maximum excretion in the first hour after ingestion of 5 Gm. of urea in thirty-eight normal men and women, a number of persons having albumin and casts, or albumin alone, in the urine showed a maximum excretion of urea in the third to the fourth hour, although blood chemical values and excretion of phenolsulphonphthalein remained normal. In orthostatic albuminuria, such a delay did not occur. A slowing of the rate of elimination of urea followed the removal of one kidney from each of six rabbits. This delayed excretion continued even four months after operation, although at no time did the animals show other evidence of disturbed function of the kidneys. A similar condition was found in a man who had had a unilateral nephrectomy performed following an accident. Our observations show that the rate of elimination of urea is a much more sensitive index of function of the kidneys than the tests ordinarily employed.

THE INFLUENCE OF FREQUENT INTRAVENOUS ADMINISTRATION OF PHOSPHATE SOLUTIONS ON NORMAL AND NEPHRITIC DOGS. A. BOLLIGER, Detroit. (Introduced by E. D. Plass.)

THE PREVENTION OF EXPERIMENTAL EFFUSIONS BY THE PARATHYROID HORMONE. HARRY GOLD, New York.

EVIDENCE OF A KIDNEY-SUPRARENAL INTERRELATIONSHIP. DAVID MARINE, New York. (Presented at the Joint Session of the Federation of American Societies for Experimental Biology.)

The demonstration of a direct venous connection between the suprarenal medulla and the kidney by Cow and the occurrence of suprarenal enlargement in cases of chronic nephritis have for many years aroused the suspicion of a functional relationship between kidney and suprarenal. Recently, the MacKays demonstrated that nephrectomy causes a distinct hypertrophy of the suprarenal cortex in rats, and Marshall and Davis (1916) demonstrated serious injury to renal function following suprarenalectomy in cats as evidenced by urea, uric acid and creatinine retention. This observation has been confirmed on dogs, cats and rabbits many times. Morphologically, the kidney of the cat shows the most striking changes, although the kidneys of the dog, rabbit and rat appear to differ only in degree. The kidneys enlarge, due mainly to swelling of the cortex which in the cat becomes softer, thicker and changes from a yellowish brown to a bright yellow. Microscopically, the appearance of such a kidney is that of an acute tubular nephritis or nephrosis. The epithelium of the tubules is swollen, vacuolated and often disintegrated. With sudan III the tubular epithelium stains almost solid orange red. This fatty change begins in the epithelium of the convoluted tubules and spreads to the descending and the ascending loops and even to the collecting tubules. The fatty metamorphosis is much milder in the rabbit and rat than in the cat, and this may be related to their longer period of survival after suprarenalectomy. It is possible that the increased production of heat which occurs in rabbits beginning from the third to the sixth day after suprarenalectomy may be secondary to the renal injury rather than dependent on the withdrawal of some influence of the suprarenal cortex per se.

What, if any, bearing these renal changes have on the problem of nephritis in general and on certain of the toxemias of pregnancy in particular at present can only be surmised. The facts that other hormones like thyroxin, pituitary, epinephrine and parathyrin are known to influence renal secretion and that the removal of no other gland produces such striking morphologic and functional changes in the kidney at least suggest some important functional interrelationship.

THE INACTIVATION OF A BACTERIOPHAGE BY MONOCHROMATIC ULTRAVIOLET LIGHT. F. L. GATES and R. MUCKENFUSS, New York. (Presented at the Joint Session of the Federation of American Societies for Experimental Biology.)

The incident energies required to kill *Staphylococcus aureus* or to inactivate its homologous bacteriophage have been measured at the various wave lengths of the quartz mercury arc between 238 and 302 millimicrons and found to run strictly parallel, the readings for the *S. aureus* phage being obtained at a uniformly higher energy level. This difference in levels is of less significance than the complete similarity in the shapes of the energy curves, which indicates that in both instances the same organic structures are adsorbing the radiations and that the fundamental reaction is the same.

The results are open to three interpretations. The most obvious is that the bacteriophage is a submicroscopic organism. Again, it is possible that the bacteriophage is a product of its own lytic action on the homologous bacterium and contains those essential structural units which in *S. aureus* also are affected by ultraviolet light and thus cause the death of the organism. A third more remote possibility is that the bacteriophage of wholly unknown nature is adsorbed on *S. aureus* material in so intimate a bond that the alteration of this material by irradiation renders the bacteriophage incapable of further self-propagation or lytic activity.

DEMONSTRATION: SPIROCHETOSIS OF THE CENTRAL NERVOUS SYSTEM IN GENERAL PARALYSIS. ROBERT R. DIETERLE, Ann Arbor. (Introduced by A. S. Warthin.)

This exhibit of microscopic preparations, photomicrographs and transparencies illustrated the subject matter of the paper already reported in this program.

DEMONSTRATION: VISCERAL SYPHILIS; MICROSCOPIC CHANGES AND SPIROCHETOSIS. A. S. WARTHIN, Ann Arbor.

Numerous microscopic preparations and photomicrographic enlargements were used to illustrate the researches of the demonstrator on the lesions of visceral syphilis and on the staining of the organisms in such lesions.

RELATIONSHIPS BETWEEN RELAPSE STRAINS OF SPIRONEMA RECURRENTIS. HENRY E. MELENEY, Nashville, Tenn.

The Chinese gray squirrel, *Sciurotamias davidianus*, when inoculated with the louse-borne spirochetes of relapsing fever, developed a heavy infection lasting from two to five days, but had no relapse. When the spleen was removed the initial infection was still heavier, and one or two relapses usually occurred. Strains recovered in relapses, when inoculated into fresh splenectomized squirrels, also produced relapses. By transferring the original strain and the various relapse strains to separate series of squirrels, six different strains were isolated which were immunologically distinct from one another, and which retained their individuality throughout the period of study. The original strain was followed for 132 days through thirty-eight transfers; the strain last isolated, for twenty-two days through six transfers. The sequence of strains appearing in relapses was not always the same. In some cases new strains appeared; in other cases there was reversion to an older strain.

It was found that strains which appeared in alternate attacks showed a definite relationship to each other. This was demonstrated by the fact that the blood of animals after an attack with strain III, IV or V sometimes contained agglutinins for an earlier isolated strain as well as for the strain responsible for the attack. Strain III was found to be related to strain I, strain IV to strain II. Strain V to both strain II and strain III, and strain VI to both strain III and strain IV.

On this basis, the occurrence of successive relapses in infections with *S. recurrentis* would seem to be due to the survival after each crisis of those spirochetes which are able to alter their biologic affinities most markedly. This mechanism produces spirochetes in the first relapse which are most different immunologically from those of the first attack, and in the second relapse spirochetes which are most different from those of the first relapse. The spirochetes of the second relapse are therefore somewhat similar to, but not identical with, those of the first attack. Relapses will continue to occur as long as the surviving spirochetes are not entirely inhibited from multiplication by the immune substances present in the blood of the host.

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, April 9, 1928

DALLAS B. PHEMISTER, *President, in the Chair*

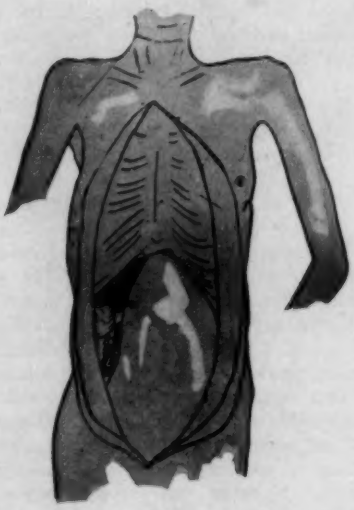
POSTOPERATIVE SERUM CHANGES IN EXOPHTHALMIC GOITER. WILLIAM F. PETERSEN and LINDEN SEED.

During the course of an examination of 100 normal persons, together with a group of patients at the Research Hospital, we have had occasion to study the blood

chemistry, the skin reactions and the general clinical condition of a small group of patients ill with exophthalmic goiter both before and after operation.

In the patients with goiter (as contrasted to the normal persons) the skin capillaries are more permeable and the time of blister formation is shortened; the electrical resistance of the skin is less; the red flare about an intracutaneous injection of thyroxin is increased while the caffeine flare seems lessened in extent. The patients have a relatively high serum calcium and potassium (the K/Ca ratio is unchanged), a high globulin and a slightly lower carbon dioxide combining power.

After removal of the gland (including both upper parathyroids), the permeability is diminished, the blister time prolonged, and the electrical resistance increased. In addition we have noted that the erythema following the application of ice and the erythema following irradiation with the Kromayer lamps is shortened in time of appearance. The red flare resulting from the intracutaneous



When the abdomen was opened, the stomach occupied practically the entire abdomen and the small bowel was in the small pelvis; there was gastro-enteroptosis and enteroptosis.

injection of epinephrine is increased in size, diminished with morphine and thyroxin, and increased with caffeine. The serum level of calcium and potassium diminish markedly, but the ratio is unchanged. Globulins are diminished and the carbon dioxide combining power is increased.

In some patients in whom the basal metabolic rate remains unchanged after operation, the skin manifestations may be altered; in other patients in whom the basal metabolic rate is lowered, the skin manifestations may be intensified. We assume that factors other than those that are involved in the change in basal metabolic rate play a rôle in the disease manifestations.

JOINT SEQUESTRA IN OSTEOMYELITIS. ETHELBERT SPURRIER.

When bone along an articular surface becomes necrotic because of osteomyelitis, it separates as a sequestrum. The sequestrum is denser than the adjacent living bone which undergoes atrophy of disuse; the articular cartilage disappears because of digestion by the proteolytic ferments liberated in the joint; the articular

cortex of the sequestrum is preserved because of its inaccessibility to chronic granulation tissue on either side; and the articular cartilage and cortex are usually lost in the remaining living portion of the joint. These changes give the sequestrum of the point a characteristic appearance which is readily recognized in roentgen-ray pictures as well as by gross examination.

EXPERIMENTAL PRODUCTION OF GLOMERULONEPHRITIS BY INTRARENAL TUBERCULIN REACTIONS. ESMOND R. LONG.

Previous studies have shown that most if not all tissues of the tuberculous animal are hypersensitive to tuberculin. The testis appears to be the most sensitive, the skin next, the lung perhaps next, and the other organs sensitive in lesser degree. In highly sensitive tissues the following acute changes are regularly noted after injection of tuberculin: hyperemia, interstitial exudation and necrosis. These are followed by absorption with atrophy or scar tissue replacement.

These two phases are striking in the tuberculin reaction of the testis. Changes analogous to these two phases are seen in spontaneous acute and chronic glomerulonephritis. It therefore seemed possible that these two types of renal lesions might be produced experimentally by inducing tuberculin reactions in the kidneys of tuberculin-sensitive animals. This organ, through the vascular filtering action of the glomeruli, lends itself exceptionally well to a study of this character. An attempt was therefore made by Miss L. L. Finner, Mr. P. J. Patchen and myself to concentrate the action of tuberculin on the glomeruli of tuberculous animals by perfusion.

Swine were chosen. These animals develop a mild tuberculosis when infected with the human type of tubercle bacillus, at the same time becoming moderately sensitive to tuberculin, and possess large renal arteries permitting easy perfusion. Three tuberculous and three normal swine were used. The perfusions were carried out in the following manner. Small amounts of the specifically active protein of tuberculin prepared by Dr. Seibert were dissolved in alkaline citrate solution and reprecipitated by the addition of a small amount of hydrochloric acid, after which the solution was again almost neutralized. The protein remained in fine suspension. An apparatus similar to that recently described before this society by Apfelbach was used for the perfusion. Amounts of from 50 to 100 mg. of tuberculin protein in a volume of about 100 cc. were then allowed to run into the renal artery at pressures from 10 to 20 mg. of mercury above the blood pressure. The animals were under ether anesthesia. More or less severe symptoms of shock regularly developed in the tuberculous animals, while no symptoms of moment occurred in the normal. The animals were observed over a period of a year and the course of anatomic and functional change followed by biopsies, nephrectomies and chemical examination of the blood.

The results were as follows: In tuberculous swine an acute exudative glomerular nephritis or at times a severe acute interstitial nephritis, occurred in the course of a few days following the injection. Within two months endothelial and epithelial organization of the exudate within the space between the glomerular tuft and Bowman's capsule resulted in a subacute proliferative glomerulonephritis. In one year practically complete recovery occurred, only a small amount of glomerular scarring persisting. The pigs used in the experiment were young animals with actively growing glomeruli. It is possible that more marked chronic changes might have developed in adult animals.

Functional changes paralleled the anatomic. In the subacute stage when both kidneys of a tuberculous animal had been perfused, the total nonprotein nitrogen of the blood doubled or tripled. As the acute changes subsided the blood chemistry returned to normal. In the normal animals, anatomic and functional changes in all cases were insignificant.

Whether or not this artificial production of glomerulonephritis has any bearing on the etiology of nephritis in man, still remains to be decided. It must be recalled that the tuberculin reaction is only one of many well known reactions of hypersensitiveness. It was chosen here simply as a representative of a type. The

hypersensitiveness associated with other chronic infections is responsible for reactions in other organs which are indistinguishable from the tuberculin reaction. It is possible that reactions of hypersensitiveness may affect the kidney in a variety of chronic infections when aroused by absorption of the inciting agent from foci of the disease.

ARTERIOMESENTERIC OCCLUSIONS OF THE DUODENUM WITH RUPTURE OF THE STOMACH. PAUL R. CANNON and BELA HALPERT.

The complete report will be published in the ARCHIVES OF PATHOLOGY.

DISCUSSION

GEORGE RUKSTINAT: In connection with this subject, Dr. LeCount has asked me to tell you of an enormous dilatation of the stomach we saw as the result of occlusion of the duodenum by mesenteric pressure. A woman, aged 40, had night sweats, a hacking cough, and lost 45 pounds (20 Kg.) in five weeks before entering the hospital. For the preceding three months she had had anorexia, distress after eating and retching and vomiting fifteen minutes after meals. The vomitus was clear, greenish and disagreeable in odor. A few days before entering the Cook County Hospital her distress became constant and vomiting continuous. The hospital diagnosis was pulmonary tuberculosis and achylia. Death occurred fourteen hours after admission.

At autopsy, there were the typical blue-green discolorations of the extremities seen in drug addicts. The abdomen was distended, the transverse colon hung down in the pelvis and the stomach reached to the brim of the pelvis on either side and obscured everything except a small portion of the liver in the right upper quadrant. There was a definite compression of the duodenum by the mesentery and when the mesentery was lifted, material from the stomach passed easily into the duodenum. The drawing representing graphically the condition, was made at the autopsy by Dr. LeCount.

Book Reviews

OUTLINES OF PATHOLOGY IN ITS HISTORICAL, PHILOSOPHICAL AND SCIENTIFIC FOUNDATIONS. A GUIDE FOR STUDENTS AND PRACTITIONERS OF MEDICINE. By HORST OERTEL, Strathcona Professor of Pathology, McGill University, Montreal, Canada. Price, cloth, $10 net. Pp. 479, with 132 illustrations, including 6 colored plates. Montreal: Renouf Publishing Company.

This volume is dedicated to the memory of Rudolph Virchow, pathologist; Wilhelm Wundt, philosopher; Hermann Senator, physician, and Theodor Billroth, surgeon. In the foreword, the author states clearly his purpose in writing this book. It is intended to present pathology "not as a practical or premedical subject, but as a scientific and cultural branch of knowledge"; it "endeavors to convey how problems of pathological life have arisen, and what their bearings are, rather than what their solution is." It is Oertel's opinion that "Pathology is at present less in need of individual efforts in discoveries and in new findings than of a strictly scientific, critical method"; and that it "is gradually undergoing a transformation in its concepts and methods of approach—repeating the history of other biological and exact sciences—and clearing itself of the purely individualistic (hospital) standpoint." With such a purpose it was obviously impossible for Oertel to write a textbook on pathology of the usual type whose general form was set by Matthew Baillie's "Morbid Anatomy" in 1795. Dr. Oertel's book is one of the pioneers in a method of approach to pathology which is philosophic rather than practical. Its more outstanding predecessors have been Ricker's "Pathologie als Naturwissenschaft," Berlin, 1924; and Charles Powell White's "Principles of Pathology," Manchester, 1927.

The present volume is divided into three chapters. The first deals with the conception of disease, which is developed from a historical and philosophical point of view. "Three great periods in the evolution of the conception of disease may be recognized; the Primitive and Ancient, the Renaissance, the Modern." Each of these conceptions is developed historically and critically. The modern conception of disease really began with Virchow whose greatest accomplishment did not lie in the establishment of the cell as the ultimate "vital unit," but "in the recognition of the scientific principle that physiological and pathological processes are nothing else but mechanical cell acts which with causal necessity follow environmental influences; that is, are released by stimuli. . . . It is, therefore, the sole duty of pathological science to find and explain the mechanism of cell activity in disease, and to discover the connecting bridge between physical cause and cell response. . . . Pathological lesions are therefore only morphological expressions of disproportions in relativity of values between stimuli and cells. These are expressed by structural changes in cells and cell territories, that is, in tissues." Cells in multicellular organisms are not independent entities "which, through union and effective cooperation, create higher organisms, but to the contrary," they are "a subordinated formal expression of an organic integrative system whose differentiation to cells and arrangement to cell territories is a function of the whole." The functional value of differentiation lies, therefore, in its integrative action. "Not the diseased cell, or the cell lesion, but its reflection upon the organism as a whole, constitute disease." Disease is defined as "a sequence of events in living individuals, as a consequence of anatomical lesions, which is reflected in the patient by symptoms which arise from disturbances thus produced in the body economy." In other words, the disease is "the subjective qualification of a lesion as displayed by the whole individual entity."

The foregoing exact quotations are presented for two purposes: First, they give some conception of the author's literary style; and second, an understanding of the author's philosophic conception of disease and the method of arriving at it are essential to a full appreciation of the remainder of the volume.

Chapter II deals with etiology. This is divided into (1) the subjective (internal) factors of disease (disposition and idiosyncrasy), under which are discussed (*a*) heredity or ancestral qualities, and (*b*) individual somatic development; and (2) objective (external) factors of disease (environment), with a discussion of physical and chemical causes, and the organized factors in the causes of disease (parasites).

In chapter III, most of the remaining subjects of general pathology are discussed under the general heading "Pathogenesis." In this chapter there are two subdivisions: Infection and Immunity, and Pathological Morphology. The latter subdivision is by far the longer and more interesting. General pathologic anatomy and histology are classified in four divisions in ascending scale of complexity of the processes concerned. This can best be given in outline, and certain features may then be commented on.

A. Disturbances in cell constitution
  (*a*) Quantitative and qualitative cell reductions
    1. Atrophy
    2. Cell disorganization and (degenerative) protoplasmic substitutions
    3. Necrosis
  (*b*) Quantitative and qualitative cell progression
    1. Hypertrophy
    2. Regeneration
    3. Metaplasia

B. Disturbances affecting tissue organization
  (*a*) Dystrophies and dystroplasias (inflammations and inflammatory growths)
  (*b*) Tissue regeneration (transplantation, regression)
  (*c*) Regressive atypical hyperplasias: tumors

C. Disturbances in circulation

D. Disturbances in organic union
  (*a*) Internal secretion
  (*b*) Fever
  (*c*) Somatic death

Section B is the most interesting division of this chapter. In the first place it is unusual that inflammation and tumors should be brought together in the same subdivision. Under the subject of inflammation, the author laments the looseness of all pathologic definitions and classifications. "Any exact definition in the natural sciences must contain and express causal relations which are obtained in logical order without regard to any metaphysical or transcendent assumptions." Oertel insists on a clear conception of the difference between scientific definitions, as already described, and metaphysical interpretations. He objects vigorously to the teleologic element in the usual definitions of inflammation, insisting that these have only a heuristic value; that is, they attempt to explain something that is unknown by means of something else which is equally unknown. Because the term "inflammation" originally connoted only a personal symptom complex or a subjective personal experience, Oertel would welcome dispensing with the word

altogether in pathology. The author apparently accepts Ricker's view and defines inflammation as "a hyperemia of variable form which depends on nervous irritation and which furnishes, according to its character, different exudations and also, according to its character, different tissue changes." This definition "has the scientific advantage of pure causality," but it has admitted weaknesses in its ambiguity and the impossibility of excluding from it other physiologic and pathologic states such as menstruation, hemorrhagic infarction and others.

Oertel's classification of tumors is relatively simple but contains nothing especially original. The discussion of the various types of neoplasms is concerned with presenting the embryologic and general histologic features rather than minutely detailed criteria for classification and diagnosis. The known facts which may have a bearing on the causation of tumors are presented in a brief but, on the whole, satisfactory manner. Factors which are associated with loss of cell and tissue balance prepare the soil for tumor growth. The local response to the presence of tumor cells in the production of a supporting stroma and a blood supply is given special emphasis.

The author's literary style is involved, often cumbersome, and sometimes not clear. The book is, therefore, "heavy reading." There are 132 illustrations, most of which were chosen to show some particular feature, and this they do reasonably well. The illustrations, however, are not the most brilliant portion of the book. This volume is printed on highly glazed paper which renders reading by artificial light somewhat troublesome. The lines on the page are slightly longer than the lines in most other textbooks of pathology, and this also adds slightly to difficulties in reading.

Oertel would separate pathology entirely from clinical medicine. Pathology is called the youngest of the sciences, but even in its undeveloped state, it must be its own reason for existence and not the fact that it is the "handmaiden" of clinical medicine and surgery. "The pathologist may not speak of diseases in the clinical sense. He never sees them. His field is not the subject, but an object, and it commences where the clinician's ends, for it consists in the recognition and scientific explanation of lesions." It is stated in the introduction that this volume "is based upon the method of teaching pathology in McGill" University. This method differs materially from that in use in many if not most other medical schools. The value of this book as a text for students will, therefore, be questioned by many. "Throughout this presentation, much more emphasis has been laid on unfolding uncertainties—that is, questions and problems—than on answers to problems." Too much dogmatism in the teaching of medical students is undesirable, but it is possible that this volume goes somewhat too far in the opposite direction. While, therefore, its value as a textbook for students may be questioned, it may be said with full justice that this is one of the most stimulating and interesting volumes on pathology that have appeared.

DIE AETIOLOGIE DER BÖSARTIGEN GESCHWUELSTE NACH DEM GEGENWÄRTIGEN STANDE DER KLINISCHEN ERFAHRUNG UND DER EXPERIMENTELLEN FORSCHUNG. By PROF. DR. CARL LEWIN. Paper. Price, 18 marks. Pp. 231. Berlin: Julius Springer, 1928.

The monograph under consideration deals almost entirely with experimental cancer research, clinical observation being drawn on only occasionally for illustration. Theory, too, has been relegated to the background for, as Lewin says, physicians have been finally delivered by experiment from the endless speculation of an earlier period. Thus, in evaluating the two main hypotheses of causation, he remarks that the embryonal cell is different from the cancer cell; whereas the

former strives constantly toward an end-stage in its growth and development, the cancer cell exhibits a purposeless and unlimited growth at variance with that of its normal prototype. Experiment having shown that cancer can be elicited in embryonal cells only under the impetus of chronic irritation, which will induce the malignant change in mature cells also, Cohnheim's embryonal rest hypothesis falls to the ground, and Virchow's irritation theory remains triumphant.

The author has succeeded in packing into a relatively few pages a discussion of the influence in etiology of light, heat, roentgen rays, radium, tar, and parasites of various sorts; of the development of sarcoma in propagable carcinomas; the transplantation of tumors into foreign species; plant "cancer"; viruses and the transmission of fowl sarcomas by cell-free filtrates; the influence of age, heredity and the endocrine glands; and, finally, of tissue culture in vitro.

The biochemical basis of malignant growth is fully considered, and after having given an extensive account of recent studies on the respiration of the malignant cell, Lewin comes to the conclusion that they still lack a firm foundation—a judgment in which those best qualified to decide will doubtless concur. In fact, he takes the sound side in practically all debatable questions, as when, for example, he adopts Orth's view that the development of a malignant tumor after a single injury is a possible but relatively uncommon occurrence. Only in respect to some current American ideas of the etiologic importance of certain micro-organisms does Lewin seem a little too hospitable.

When some six hundred references are printed, it is almost inevitable that some names should suffer, and some do, though the number misspelled is no higher than what might in these days be called the normal quota.

It is inevitable, too, that there should be omissions when an author has to compress into less than two hundred and fifty pages an amount of material sufficient to fill a large volume. But even so, one is disappointed to find in the section devoted to immunity no reference to the one paper that has done more than all others to bring order out of chaos: Russell's article on resistance to the growth of transplantable tumors, which appeared in 1912. In the discussion of athreptic immunity, too, there is no mention of the experiment of Haaland which gave the death blow to Ehrlich's elaborate hypothesis. Thanks to the work of these two men, athreptic immunity and the operation immunity of Uhlenhuth and his school have become relics possessing historic interest merely; yet their discussion occupies several pages of this monograph.

In spite of occasional lapses such as these, however, the book may be warmly recommended to all who are desirous of learning what progress has been made in the study of etiology. Here the beginner will be brought to realize that many of his newest and most brilliant ideas have been under discussion for some thirty years, while the more experienced investigator can refresh his memory of work accomplished long since and enjoy the stimulus of viewing it from the angle of a scarred and battered veteran of cancer research.

POST MORTEMS AND MORBID ANATOMY. By THEODORE SHENNAN, M.D., F.R.C.S., Edinburgh, Professor of Pathology in the University of Aberdeen. Second edition. Pp. 664, with 214 illustrations. London: Faber & Gwyer, 1927.

This is the second edition of a work that has long been out of print. According to the author, it has been rewritten and recast "with a view to making it a text-book of special pathology as well as a manual for use in the post-mortem room." It may well be doubted, however, that this newer aim will be attained, since the field is adequately covered by many established works over which this one does

not have any apparent advantage. Indeed, to the experienced pathologist, Professor Shennan's opus may appear superfluous; but to students, and particularly to "internes" in pathology, it should adequately justify its existence.

It deals primarily with the methods of postmortem examinations and with the evalution and classification of postmortem appearances. Of the twenty-one chapters, the first three are concerned with general procedures, such as choice of instruments, precautions to be taken, the external examination of the body and methods of dissection. The organs and organ-systems are then discussed in detail, the order followed being essentially that which is advocated in the actual dissection of the body. Each chapter begins with a short summary of normal anatomy, tabulations of weights and measurements and detailed instructions for dissecting. The common postmortem changes are not neglected, a feature that will be gratefully recognized by the uninitiated. There follows, then, the description of morbid processes that naturally constitutes the bulk of the volume. In general, this proceeds along orthodox lines, but enough of the author's prejudices are injected to make it agreeably controversial. The effects of various poisons are briefly covered in chapter twenty; the twenty-first includes the examination of stillborn infants and a discussion of deaths under anesthesia. An appendix outlines various technical procedures such as methods of preserving, fixing and staining tissues.

While many may not agree with the classifications adopted, they can hardly disagree with the descriptions, nor can it be urged that anything of great importance has been omitted. Everything else is made subservient to immediate sensory discrimination. Etiology and microscopic anatomy are discussed just sufficiently to render interpretations of the gross intelligible. In the main, theory is dismissed, the author evidently believing that it is better to observe than to speculate, at least in the postmortem room. Glittering generalities are wisely avoided.

That the contents of this book are largely the fruit of the author's own experience is evident throughout, despite his acknowledged Edinburgh bias. Inherent in this individual make-up is the often unduly long quotation of a personally observed case, a defect no less common to pathologists than to clinicians. References to the literature are confined almost entirely to recent contributions. The illustrations leave much to the imagination, in many instances being depressingly ambiguous. A few colored plates would add enormously to the text. But aside from these minor disappointments, the author's designs are well served; the real and valuable function of the book is that of a connecting link between what the novice sees at autopsy, and what Professor Shennan has seen and pondered over during the course of his abundant experience.

KONSTITUTIONSPATHOLOGIE IN DER ORTHOPÄDIE. ERBBIOLOGIE DES PERIPHEREN BEWEGUNGSAPPARATES. By BERTA ASCHNER and GUIDO ENGELMANN, with introduction by JULIUS BAUER. Paper. Price, 28 marks. Pp. 312, with 80 illustrations. Berlin: Julius Springer, 1928.

A general outline of the principles and mechanism of heredity and of the intrauterine factors influencing fetal development precedes the chapters dealing directly with orthopedic deformities. The constitutional aspects of each condition are presented with a review of the literature, with charts showing the incidence of the deformity, and sometimes of related anomalies, in succeeding generations, and with a discussion based on the introductory outlines. The fifteen main headings include: numerical variations of the skeletal system (polydactylism, syndactylism etc.), disturbances of cartilaginous growth (3-phalangeal thumb, chondrodystrophy, etc.), epiphyseal disturbances (Madelung's deformity, Perthes' disease, and others), deformities of the spine (scoliosis, hetedotraumatic kyphosis, chronic spondyl-

arthritis), congenital contractures, luxations, retarded and atavistic development, and congenital abnormal conditions of muscle, fascia and synovial membranes. Scoliosis, for example, is considered in three groups: congenital scoliosis, with special reference to the forms due to assymetrical intra-uterine development; scoliosis associated with rickets; and scoliosis resulting mechanically from other malformations. In all groups, the constitutional factor is indicated by records of inheritance which were obtained in as high as from 25 to 30 per cent of the cases of scoliosis with rickets. The question as to which is heritable, the disposition to rickets or to scoliosis, leads to the conclusion that the genotype representation of abnormal development of the spine may become apparent only when rickets intervenes. The discussions assume a genotype representation for each organ and part of an organ, a gene for normality opposed by a gene for abnormality (as for Thomsen's myotony), and a gene for localization which, if disturbed, leaves other influences, either hereditary or environmental, unresisted, or which leads directly to retarded development of the part. This review with its index and large bibliography is of interest both for persons studying the clinical conditions and for those seeking newer fields for investigation.

DIE WICHTIGSTEN KRANKHEITEN DES KANINSCHENS MIT BESONDERER BERÜCKSICHTIGUNG DER INFECTIONS- UND INVASIONSKRANKHEITEN VON PRIVATDOZENT OSKAR SEIFRIED, M.D., Abteilungsvorsteher am Veterinärhygienischen- und Tiereuchen- Institut der Universität Giessen. Price, 15 marks. Pp. 160, mit 54 Abbildungen im Text. München: J. F. Bergmann, 1927.

Undoubtedly the rabbit owes its position as one of the most used laboratory animals more to the fact that it is a prolific, long-eared pacifist than to any outstanding suitability. What with spontaneous cirrhosis, nephritis, arteriosclerosis and encephalitis, to say nothing of a marked susceptibility to epidemic respiratory infections, hemorrhagic septicemia and innumerable parasites, it is, on the whole, one of the most treacherous of all experimental animals. The systematic discussion of the natural diseases of the rabbit is well worth while, and this monograph is to be recommended to all who use rabbits in experimental work. The subject is well covered with adequate bibliography, not limited to German literature, American work on tularemia and other diseases of rabbits receiving consideration.

MANUALE ATLANTE DI TECNICA DELLE AUTOPSIE. By PROFESSOR ENRICO FRANCO. Price, 80 lires. Pp. 456. Messina: Casa editrice Giuseppe Principato, 1926.

This is a well written book on the technic of postmortem examination illustrated by a large number of simple and clear drawings. The author follows the Virchow technic in removing each organ separately from the body before cutting it. In modern pathology, however, there is an increasing tendency to keep the topographic relations as long as possible, leaving the separation of the organs until the end of the necropsy. Some of the author's methods are too radical to be applicable in this country. A complete list of the size and weight of the organs at different ages is attached to the text. With a fair reading knowledge of the Italian language, one will obtain valuable informations from Franco's manual.

Books Received

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. Volume IX. Communicable and Other Diseases. Prepared Under the Direction of Major Gen. M. W. Ireland, the Surgeon General, by Lieut. Col. Joseph F. Siler, M.C., U. S. Army. Pp. 628. Washington: U. S. Government Printing Office, 1928.

A TEXT-BOOK OF INFECTIOUS DISEASES, being the Third Edition of Goodall and Washbourn's Manual of Infectious Diseases. Revised and in large part re-written by E. W. Goodall, O.B.E., M.D., B.S., London. Price, $10. Pp. 718, with 26 plates (including 6 colored) and other illustrations, 15 diagrams and 34 charts. New York: William Wood & Co., 1928.

UEBER DAS PROBLEM DER BÖSARTIGEN GESCHWÜLSTE. Eine experimentelle und theoretische Untersuchung. Von Professor Dr. Lothar Heidenhain. Price, 28 marks. Pp. 153, with 141 illustrations. Berlin: Julius Springer, 1928.

MEDICAL RESEARCH COUNCIL. An Inquiry Into the Relationship Between Housing Conditions and the Incidence and Fatality of Measles. By James L. Halliday, M.D., D.P.H. Special Report Series, no. 120. Price, 1 shilling, net. Pp. 34. London: His Majesty's Stationery Office, 1928.

PATHOLOGISCHE ANATOMIE, EIN LEHRBUCH FÜR STUDIERENDE UND ÄRZTE. Von L. Aschoff, M. Askanazy, H. Breitzke, C. Benda, W. Berblinger, M. Borst, A. Dietrich, P. Ernst, A. Ghon, E. von Gierke, Georg B. Gruber, L. Jores, O. Lubarsch, O. Naegeli, R. Rössle, M. B. Schmidt, H. Schridde. Herausgegeben von L. Aschoff. I. Band: Allgemeine Ätiologie allgemeine pathologische Anatomie. Price, 37 marks. Pp. 853, with 475 illustrations. II. Band: Spezielle pathologische Anatomie. Price, 42 marks. Pp. 1061, with 686 illustrations. Seventh edition. Jena: Gustav Fischer, 1928.

PATHOLOGISCHE ANATOMIE DER TUBERKULOSE. Von P. Huebschmann, o. Professor, Direktor des Pathologischen Instituts der Medizinischen Akademie in Düsseldorf. Price, 86 marks. Ph. 516, with 108 illustrations. Berlin: Julius Springer, 1928.

FILTRABLE VIRUSES. By Harold L. Amoss, Jacques J. Bonfenbrenner, Alexis Carrel, Edmund V. Cowdry, Rudolf W. Glaser, Ernest W. Goodpasteure, Louis O. Kunkel, Stuart Mudd, Peter K. Olitsky, Thomas M. Rivers. Edited by Thomas M. Rivers. Cloth. Price, $7.50. Pp. 414, with 27 illustrations. Baltimore: Williams & Wilkins Company, 1928.

A TEXT-BOOK OF GENERAL BACTERIOLOGY. By Edwin O. Jordan, Ph.D., Professor of Bacteriology in the University of Chicago and in Rush Medical College. Ninth edition. Cloth. Price, $6. Pp. 778, with 191 illustrations. Philadelphia: W. B. Saunders Company, 1928.

The first edition appeared in 1908. The present edition has been revised thoroughly. The chapter on parasitic protozoa has been rewritten. The book continues to be an adequate and reliable text on general bacteriology, succinct yet fully abreast of current knowledge and a classic model in manner and style of presentation.

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